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THE PROBLEM OF UNSUSPECTED TUBERCULOSIS IN PREGNANCY

INCIDENCE BY ROENTGENOLOGIC TECHNIQUES COMPARED WITH INCIDENCE OF UNSUSPECTED SYPHILIS

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WHEN pregnancy occurs in a woman who has tuberculosis, a serious problem confronts the physician. Although opinions differ concerning methods of treatment, there is common agreement as to the seriousness of the condition and as to the necessity for close supervision of the patient by both obstetrician and internist. In most instances, the woman with active tuberculosis should not undertake the added burden of pregnancy, both because of the risks incurred during gestation and because of the post-partum implications to both mother and child. To avoid disaster, the tuberculous woman who does become pregnant requires the best obstetric and medical care that is obtainable. As an obvious corollary to this, recognition of the disease is essential before the pregnant woman can benefit from this special medical attention; the earlier during pregnancy that the disease is discovered, the better is the outlook for the patient. As Schwarz[1] has said ". . . it must be borne in mind that unrecognized active tuberculosis in pregnancy will progress

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rapidly in the untreated state. Therefore it is important to recognize early active lesions.''

It has become well recognized that dependence on the presence of symptoms and of abnormal physical findings is frequently quite inadequate for the detection of pulmonary tuberculosis. Many cases of tuberculosis reach an advanced stage before any symptoms are produced, and it is the exceptional case in which minimal lesions produce notable symptoms. Only rarely do symptoms occur until the disease has advanced into the stage of tissue necrosis. It is significant that more than 80 per cent of all cases of tuberculosis reported to health departments are already in an advanced stage.[2]

The inadequacy of even the most skilled physical examination in detecting the presence of pulmonary tuberculosis likewise has become a widely accepted fact.

Kayser-Petersen's[3] extensive review indicated that from 10 to 60 per cent of all cases of tuberculosis found on x-ray examination had been missed on physical examination. Bloch[4] estimated that more than one-third of all cases of clinically important chest disease are missed on physical examination. He now believes that this estimate is too conservative. Sampson and Brown[5] carefully studied 1,004 patients with tuberculosis at the Trudeau Sanitarium. They found no physical signs of disease in 39.6 per cent of the patients and physical signs indicating less disease than the roentgenogram in an additional 36 per cent.

Thus, it would seem to be evident that physical examination of the chest alone should be eliminated as a reliable tuberculosis case-finding method.

In recognition of the above considerations, fluoroscopy of the chest was introduced as a routine procedure for the patients attending the prenatal clinic of the Chicago Lying-in Hospital in 1934. All patients were invited to attend the chest clinic of the University of Chicago Clinics where the examination was made without charge. The fluoroscopies were performed by members of the staff of the chest division. Patients having definite or suspected lesions at fluoroscopy were referred for stereoscopic chest roentgenograms and for further investigation in the chest clinic. Due to difficulties in inducing patients to make a special trip to the clinics for fluoroscopy, only 64 per cent of the clinic group were fluoroscoped during the first three years of the program. When the results of these three years were compiled, the incidence of 1.06 per cent of unsuspected clinically important tuberculosis found by fluoroscopy seemed so important that efforts were made to extend the survey to all patients attending the prenatal clinic. Since it was agreed by the obstetricians and internists concerned that this program was beyond the experimental stage, plans were made to include routine chest fluoroscopy as a permanent part of the regular prenatal care. Since February, 1941, a fluoroscopy room staffed by members of

the chest division and physicians trained by the chest division has been an integral part of the prenatal clinic, and all patients are fluoroscoped as a part of their initial examination. Those found to have definite or suspected lesions, in addition to those patients with known tuberculosis or with tuberculosis discovered at the initial examination by history taking and/or physical examination are referred directly for stereoscopic roentgenograms.

MATERIAL AND RESULTS

The patients attending the prenatal clinic are all of the white race. Although none of them are private patients, they do not represent the lowest economic strata inasmuch as most of them pay for at least part of their obstetric care and most of them are delivered in the hospital, usually paying part or all of the hospital fees.

The average age of the patients fluoroscoped during pregnancy was 25.8 years, with a standard deviation of 5.5 years. The distribution by age groups of the 6,928 women examined between 1937 and 1941 was as follows:

AGE GROUP	NO.	PER CENT
15-19 years	665	9.6
20-24 years	2,543	36.7
25-29 years	2,113	30.5
30-34 years	1,108	16.0
35-39 years	395	5.7
40-44 years	104	1.5
Totals	6,928	100.0

Incidence of clinically important tuberculosis was found to rise with age, as has been found to be the case in other studies. This was especially true of *active* tuberculosis, less true of inactive clinically important tuberculosis, where a definite peak was found in the thirty to thirty-four age group. These findings are illustrated in Fig. 1.

Recognizing the importance of the discovery of tuberculosis as well as of other factors complicating pregnancy as early as possible during gestation, obstetricians have for years stressed the desirability of patients reporting to their physician in the early months of pregnancy. An analysis of the 6,928 women examined between 1937 and 1941 as to the stage of gestation at which they first reported to the prenatal clinic, and when, therefore, they had their initial chest fluoroscopy, shows that the average woman reported when she was 4.53 months pregnant. The distribution of the stage of gestation at the time of first examination is shown graphically in Fig. 2. Similar analysis of those patients found to have clinically important tuberculosis revealed that there was a tendency for these cases to report somewhat later in the gestation period on the average than did the entire group. The figures were as follows:

	PER CENT EXAMINED IN		
	FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER
Total group (6,928 cases)	37.9	42.1	20.0
Clinically important tuberculosis	25.4	52.2	22.4

It will be noted that approximately 3 of 8 women were initially examined in the first trimester, when therapeutic abortion may best be done when indicated, but that only approximately 2 of 8 women found to have clinically important tuberculosis were initially examined at this stage. In not all women with clinically important tuberculosis is therapeutic abortion advisable or necessary, but the lateness of diagnosis in the period of gestation proved an obstacle to the optimum management of an appreciable number of cases. Therapeutic abortion was performed two times in this series and advised in an additional patient. Sterilization was done four times and advised in three additional patients.

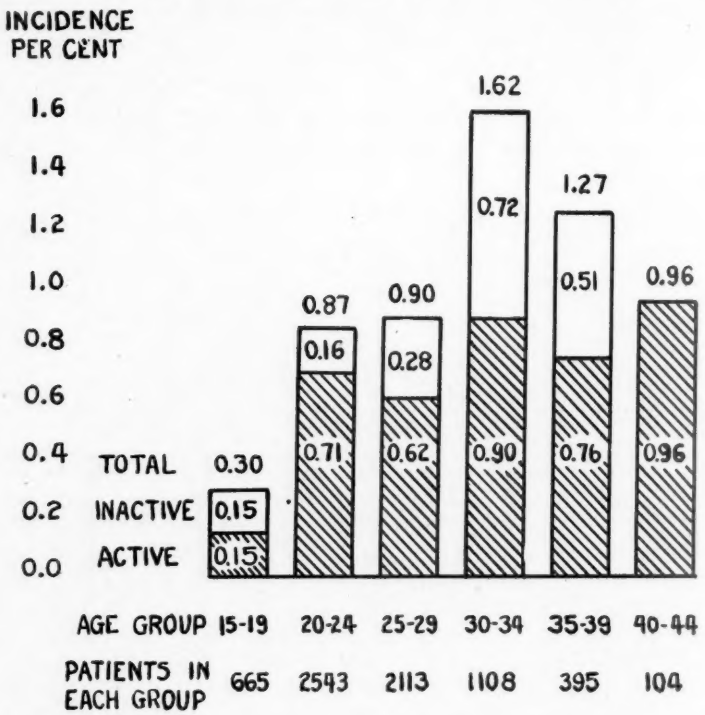

Fig. 1.—Incidence by age of unsuspected clinically important pulmonary tuberculosis, active and inactive, showing the increasing incidence with age, particularly of active tuberculosis.

The results of the prenatal fluoroscopic survey covering the period from Feb. 14, 1934, to April 1, 1937, have been reported in this JOURNAL.[6] The present study presents the data for the period from April 1, 1937, to July 1, 1941. The data of both periods are presented in parallel columns (I and II) and are summarized in Column III of Table I. Although routine chest fluoroscopy provides valuable working information in conditions other than tuberculosis, notably in heart disease, for purposes of this paper only tuberculous lesions will be considered.

The classification of tuberculous lesions is subject to numerous variations. For practical purposes, we have divided the lesions discovered at

fluoroscopy into *clinically important* and *clinically unimportant* tuberculosis. The clinically important tuberculosis was further divided into *active* and *inactive* lesions. The classification of each case was made on the basis of a survey of all facts known concerning the patients, clinical, laboratory, and x-ray, by a team of two or three consulting physicians.

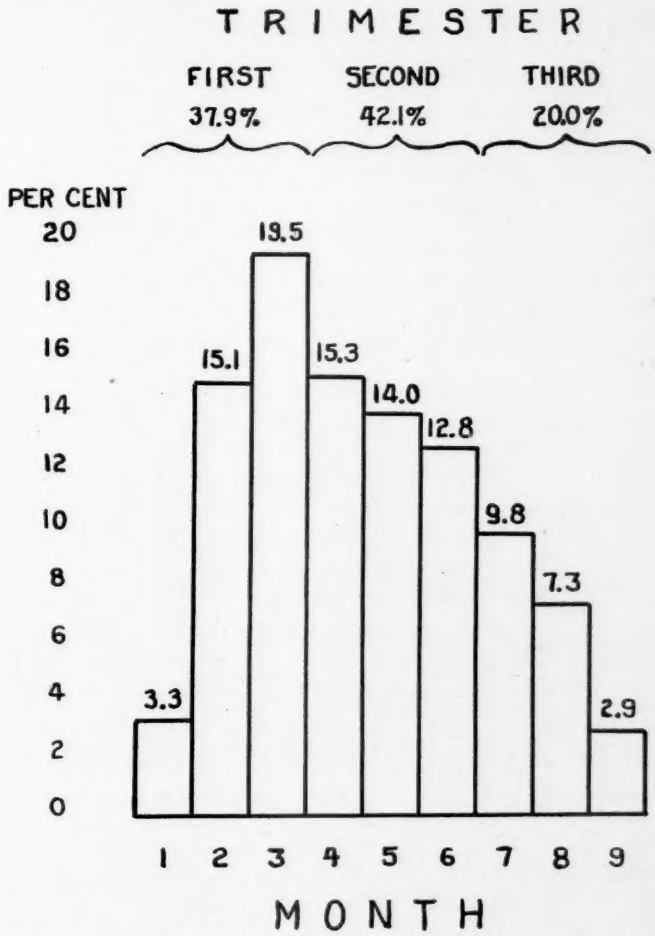

Fig. 2.—Distribution of stage of gestation when patients appeared for initial prenatal and fluoroscopic examination.

The patients classified as having clinically important tuberculosis include those with active disease, and those with the disease in an inactive stage but such that reactivation during pregnancy or the puerperium is a definite menace. Such cases will include those patients without symptoms or physical findings but who are found on x-ray examination to have tuberculous lesions which do not as yet give satisfactory evidence of healing by fibrosis and/or calcification. All of the patients in this classification are followed closely and their physical activities are

TABLE I. INCIDENCE OF UNSUSPECTED AND KNOWN TUBERCULOSIS AND SYPHILIS IN PREGNANT WOMEN AT CHICAGO LYING-IN HOSPITAL, IN THE PERIODS 1934 TO 1937 AND 1937 TO 1941

	I PREVIOUSLY REPORTED DATA FEB. 14, 1934 TO APR. 1, 1937			II PRESENT STUDY APR. 1, 1937 TO JULY 1, 1941			III SUMMARY OF ENTIRE SERIES 1934-1941		
	NUMBER	PER CENT FLUOR. PTS.	PER CENT CLINIC PTS.	NUMBER	PER CENT FLUOR. PTS.	PER CENT CLINIC PTS.	NUMBER	PER CENT FLUOR. PTS.	PER CENT CLINIC PTS.
Patients attending the prenatal clinic	6,298		100	8,808		100	15,106		100
Patients fluoroscoped	4,040		64	6,928		79	10,968		73
Tuberculosis:									
Unsuspected tuberculosis of clinical importance discovered by routine fluoroscopy									
Active	28	0.69		46	0.66		74	0.67	
Inactive	15	0.37		21	0.30		36	0.33	
Total	43	1.06		67	0.96		110	1.00	
Known tuberculosis (including tuberculosis discovered by methods other than fluoroscopy)	49			50*			99		
Total tuberculosis	92		1.46	117		1.33	209		1.38
Syphilis:									
Unsuspected syphilis (discovered by routine Wassermann and Kahn tests)	55		0.87	27†		0.30	82		0.54
Known	·39		0.62	64‡		0.73	103		0.69
Total syphilis	94		1.49	91		1.03	185		1.23

*Eighteen additional cases of known tuberculosis delivered in the hospital, 9 private patients and 9 patients who did not attend prenatal clinic.

†Thirteen of these patients were discovered to have syphilis during this pregnancy elsewhere before coming to prenatal clinic. There were 8 additional patients with syphilis delivered in the hospital, 4 private patients and 4 who did not attend prenatal clinic.

‡In addition there were 2 private patients and 10 hospital patients with known syphilis.

restricted according to the needs of the individual case. Naturally, the patients with active disease give the greatest concern.

The group of patients with clinically unimportant disease includes those with calcified and calciocaseous lesions which appear to be healed, and minimal fibroid lesions which appear inactive. In general, included in this category are lesions which, after investigation and observation, show satisfactory x-ray criteria of healing and are thought to manifest little likelihood of reactivation due to pregnancy. There were 62 patients in this group, and they were judged to require no special treatment. This group did not include individuals with a calcified primary complex although these are considered to be clinically unimportant. For the most part, such primary calcifications are recognized and identified at fluoroscopy and further study is not made.

The incidence of unsuspected tuberculosis of clinical importance discovered by this survey has remained nearly the same during the second period (0.96 per cent) as it was in the first reported period (1.06 per cent). The slight decrease of 0.1 per cent may well be attributed to statistical limitations. However, a factor was operating which would tend to decrease the incidence, namely, the dilution of the fluoroscoped group by the ever-increasing number of re-examinations of healthy subjects during recurring pregnancies. That is, during each year that the program operates, there is included a progressively increasing number of women who have been found by fluoroscopy to be free of clinical tuberculosis in previous pregnancies. (Those discovered to have tuberculosis are included in the group of known cases in any subsequent pregnancies.) During the calendar year of 1940, 18.6 per cent of the women fluoroscoped had been examined by us in one or more prior pregnancies. We conservatively estimate that during the second period of the survey, 10 per cent of the 6,928 women examined were repeaters. If these 693 were deducted from the total, the incidence of unsuspected tuberculosis would be 1.07 per cent, a figure essentially identical to that of the first period.

DISCUSSION

What is the significance of discovering that approximately 1 per cent of our prenatal patients have unsuspected clinically important tuberculosis? As a means of estimating the value of the present case-finding program, we have compared our data with the incidence of tuberculosis in pregnant patients reported from several hospitals and maternity centers where tuberculosis case-finding programs were not employed. The social and economic status of the patients in most of these groups appears to be equal to or lower than that of the patients in our series. These data are summarized in Table II. In 82,472 obstetric patients, only 55 were found to have tuberculosis, an incidence of 0.067 per cent. The 1 per cent unsuspected tuberculosis discovered in our patients by routine fluoroscopy represents an incidence 15 times greater.* It is even more striking that the incidence of *active tuberculosis* found in our survey is *ten times greater* than that found in similar groups where case-finding methods were not used. It is therefore a fair inference that 90 per cent of all active tuberculosis is missed by not employing some effective case-finding program. Where else in medicine is a 90 per cent diagnostic error tolerated when simple, adequate methods are available for elimination of the error?

Routine serologic tests for syphilis in pregnant women have come to be regarded as a medical necessity, and in some states as a legal necessity. Today, no one questions the wisdom of this procedure. In our first report,[6] we compared the incidence of unsuspected syphilis discovered in the prenatal clinic by routine Wassermann and Kahn tests with the

*In our series, there were 99 additional patients with known tuberculosis.

TABLE II. THE INCIDENCE OF TUBERCULOSIS IN OBSTETRIC PATIENTS IN INSTITUTIONS NOT EMPLOYING CASE-FINDING METHODS

AUTHORS	INSTITUTION	NUMBER OF OBSTETRIC PATIENTS	PER CENT WARD OR CHARITY PATIENTS	NUMBER OF CASES OF TUBERCULOSIS	INCIDENCE OF TUBERCULOSIS (PER CENT)
Allen and Bauer[7] Chicago, Ill.	Rush Home Service and Presbyterian Hospital	9,696		7	0.07
Fox[8] Oak Park, Ill.	West Suburban Hospital	7,628		11	0.14
Kushner[9, 10] New York	Bronx Hospital	3,166	100%	0	0.00
Levine and Warrick[11, 12] Brooklyn, N. Y.	Beth El Hospital	13,600	33	1	0.01
Potter[13] Orange, N. J.	Orange Memorial Hospital	10,000	23	3	0.03
Tamis and Clahr[14] New York	Morrisania Hospital	1,009	100	0	0.00
Tisdall[15] Brooklyn, N. Y.	St. Catherine Hospital	19,634	15	15	0.08
Tucker[16] Chicago, Ill.	Chicago Maternity Center	17,739	100	18*	0.10*
Total		82,472		55	0.067

*The 18 cases of Tucker include 8 cases in which tuberculosis was suspected but not proved due to the patients failing to return.

The data of Royston, Jensen and Hauptman[17] (St. Louis Maternity Hospital and O.P.D.) are omitted from the table. Some of their patients (number not stated) were referred to them for delivery because of known tuberculosis, and the authors point out that their figures therefore do not represent a true incidence of tuberculosis. Of 13,570 patients, 51, or 0.37 per cent, had tuberculosis. Of the patients with tuberculosis, 37 per cent were negroes.

incidence of unsuspected tuberculosis discovered by routine fluoroscopy. There was a striking similarity in the two figures, 0.87 per cent for unsuspected syphilis and 1.06 per cent for unsuspected tuberculosis. In the present study, a similar investigation reveals a surprising change. Although the incidence of tuberculosis remains essentially the same (1.06 and 0.96 per cent), the incidence of unsuspected syphilis has dropped to a little more than one-third of its former level (0.87 to 0.3 per cent). This is shown graphically in Fig. 3. The incidence of known syphilis increased slightly (0.62 to 0.73 per cent). There is a plausible explanation for this dramatic decline in unsuspected syphilis. On July 1, 1937, the Illinois hygienic marriage law became effective, requiring, among other things, premarital serologic tests for syphilis. From July 1, 1937, to Jan. 1, 1941, a total of 189,846 blood specimens have been tested in the Illinois State Diagnostic Laboratories in compliance with this law. Of this number, 2,615, or over 1.3 per cent, were positive.[18] (These figures do not take into account the tests done in private laboratories.)

With such highly satisfactory results accruing from large scale syphilis case-finding activities, is it not reasonable to expect an equally

satisfying decrease in the incidence of tuberculosis among prenatal patients if similar laws were applied to tuberculosis case finding? Just as the discovery of syphilis before marriage protects the innocent partner as well as the offspring against syphilis, so would premarital detection of tuberculosis protect the family.

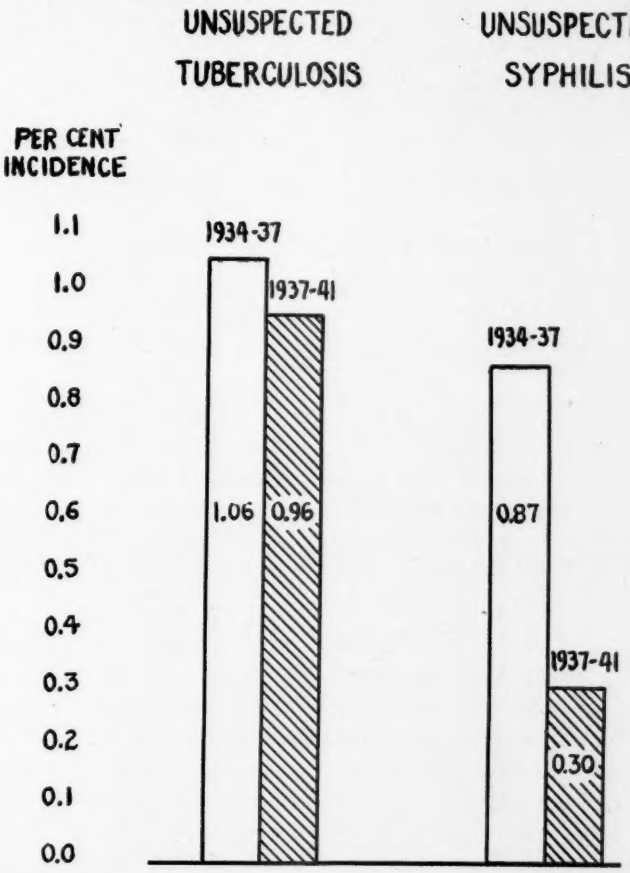

Fig. 3.—Comparison of incidence of unsuspected tuberculosis and of unsuspected syphilis in pregnant women, in the periods 1934 to 1937 and 1937 to 1941. The slight decline in the incidence of unsuspected tuberculosis in the two periods is in contrast with the marked decline in the incidence of unsuspected syphilis, following the passage of the Illinois hygienic marriage law in 1937.

"Case-finding has become the watchword in the fight against tuberculosis."[19] Recent years have seen constantly increasing activity in this field, especially among the adult population. It would seem that there is not a group anywhere more appropriate for the application of tuberculosis case finding than obstetric patients, for here the rewards of one's efforts are magnified. In the first place, the disease is discovered at a time when the human organism is undergoing an unusual strain and therefore at a time when the disease is most dangerous to the patient.

Thus, it is also at a time when appropriate treatment will be of great benefit. Second, exposure of the new-born infant may be prevented by isolation from the mother in cases where the sputum contains tubercle bacilli.

Jameson[20] has proposed that the funds spent on prenatal case finding could be used to better advantage in providing superior obstetric and medical care for the tuberculous pregnant woman, preferably in institutions organized especially for this purpose. It should be emphasized that all too often, even in the great majority of cases, the tuberculous pregnant woman is not recognized as such unless special case-finding methods are used, and therefore she cannot benefit by the special medical care proposed.

Much discussion and controversy have raged concerning the relative merits of various case-finding techniques. We believe that in the hands of well-trained personnel, chest fluoroscopy followed by roentgenograms in suspected cases is an inexpensive, accurate, and efficient method.

As Bloch[19] has said, "There is good reason to believe that very few of even small parenchymal infiltrations are overlooked by an experienced examiner who is well trained in fluoroscopic technique, in roentgen diagnosis, and in pulmonary pathology. Most of the critics of the fluoroscopic method with whom we have had personal contact betrayed a considerable lack of these requirements and offered opinions on the subject which originated either from hearsay or from an apprehension of the unknown."

Many of the figures cited to discredit the fluoroscopic method[21] include in the percentage error instances in which insufficient diagnoses were made as well as instances in which lesions were erroneously diagnosed by fluoroscopy, and subsequently disproved by roentgenograms. Such criticisms are misleading in that these latter errors are quite inconsequential, for their inclusion does not reduce the total amount of tuberculosis discovered in the group.

The studies of Israel and Hetherington[22] are noteworthy. In a series of 1,021 subjects examined simultaneously by fluoroscopy and stereoscopic roentgenograms, in only 4 among 211 cases of definite tuberculosis found by x-ray were tuberculous infiltrations of immediate clinical significance missed by fluoroscopy. They calculated that the accuracy of fluoroscopy was 99 per cent in the hands of experienced physicians and 96 per cent in the hands of physicians less well trained. Stiehm[23] believes that fluoroscopy has certain definite advantages over roentgenograms, and reports instances of fluoroscopy discovering lesions missed on stereoscopic films.

A large part of the criticism directed against fluoroscopy as a screening method is directed against the use of fluoroscopy alone (without roentgenograms of suspected lesions). With this we have no quarrel,

except that in some instances a clear distinction is not made as to which method is being criticized.

Roentgenograms offer the advantage of a permanent record and of some increase in accuracy, but in many situations it is doubtful that the slight increase in accuracy per se justifies the greatly increased expense. The several miniature roentgenographic methods recently introduced probably sacrifice accuracy to a point where it is equal to, or below, the level of accuracy of the fluoroscopic method.

There would appear to be a number of reasons why the tuberculin survey method is not as suitable for case finding in the average adult group as the various roentgenologic methods. The tuberculin method is considerably more cumbersome, in that it requires multiple visits of each patient. It has been found that numerous adult patients tested do not return for the reading of the tests, and considerable personnel is necessary for adequate follow-up work. Ianne and Muir,[24] for example, found that of 805 prenatal patients given tuberculin tests, 114 (14 per cent) failed to return for a reading, and of the 284 positive reactors, 32 (11 per cent) failed to return for roentgenograms. Douglas and Birkelo[25] found that of 1,425 prenatal patients given tuberculin tests, 144 (10.1 per cent) failed to return for the test to be read.* A second disadvantage of tuberculin surveys in adult groups, especially in metropolitan areas, is the large percentage of positive reactors, all of whom require roentgenograms. In Ianne and Muir's[24] prenatal patients (Santa Clara County Hospital, San Jose, California), 41.4 per cent were positive reactors to tuberculin, and in Douglas and Birkelo's[25] study (Prenatal Clinics of the Health Department, Detroit), 47.6 per cent reacted to tuberculin. Inasmuch as all positive reactors require roentgenograms, the cost of these added to the expense already incurred in tuberculin testing would make the total expense closely approach that of a survey using roentgenograms from the beginning. In contrast to the large percentage of roentgenograms required in tuberculin surveys, in our fluoroscopic survey, roentgenograms were made on only 3.5 per cent of the subjects. The fluoroscopic method has the great advantage of scheduling the complete examination for tuberculosis at the time of the first clinic visit, thus eliminating follow-up failures and expense.

A further objection to the tuberculin method for adults is raised by the question of accuracy. In a study correlating the tuberculin test and roentgenograms, Crimm, Potts and Hudson[26] found that "about 21 per cent of the individuals with pulmonary lesions would have been overlooked" if the tuberculin test alone had been employed. Douglas and Birkelo[25] made simultaneous tuberculin tests and roentgenograms

*Of the 10,968 fluoroscoped patients in our series, 33 (0.3 per cent of entire series, 9 per cent of x-rays ordered) failed to have the x-rays ordered at fluoroscopy. About half of these did not return for further prenatal or obstetric care. This leak has now been stopped by completing the examination, including roentgenograms, at the first visit.

on 1,425 pregnant women, using the single "middle dose" tuberculin screen. Of the 671 patients who were tuberculin-negative, there were two cases of active tuberculosis, and among the 144 patients who failed to return to have the test read, there were two additional active cases.*

Tuberculosis case-finding programs for prenatal patients have been restricted almost exclusively to clinic patients. In view of the increased danger from tuberculosis during pregnancy, and since patients in the upper income brackets are not immune to the disease, it would seem desirable that private obstetric patients also should have the benefits of modern case-finding methods. In private practice, the use of routine roentgenograms probably is the most feasible method. That such a program is actually workable and productive of worth-while results has been demonstrated by Graham.[29] Routine roentgenograms made on 800 consecutive private obstetric patients revealed 8 cases (1.0 per cent) of active tuberculosis and 24 cases (3.0 per cent) of other significant parenchymal disease.

Lest we be lulled by a false sense of security engendered by the marked decline in the tuberculosis death rate which our generation has seen, it is noteworthy that this decline is not shared equally by all age and sex groups. Wolff's study[30] of the differential decline of the tuberculosis death rate in various age and sex groups shows a striking lack of decline in the group of young adult females. As the general tuberculosis death rate decline is worldwide, so also the retarded or absent decline for young adult females is worldwide. In some countries, notably England, there has been a real increase in the mortality in this group.† Wolff suggests that this failure of young adult females to share in the favorable general mortality statistics is closely connected with childbearing and maternal activity. "Hence, it is our future task to diminish further the great risk of young women from tuberculosis mortality during the years of increased generative and maternal activity. This task is a medical one not to be solved by preventing pregnancies in young women, but by alleviating the dangers always connected with childbearing. . . ."

Tuberculosis has moved from first place to seventh place as a cause of death in the general population. But *for young women of the child-*

*Graham, Auston and Putnam[27] x-rayed and tuberculin-tested 7,493 individuals in Alabama, and Saward, Putnam and Opie[28] 1,389 in Jamaica. Among the 8,882 individuals, 2.43 per cent manifest tuberculosis was found, the incidence being 3.14 per cent in positive reactors and 0.35 per cent in nonreactors. Including also tuberculosis found on x-ray without symptoms, the incidence of combined manifest and latent apical tuberculosis was 4.89 per cent, or 6.35 per cent among positive-reactors and 0.66 per cent among nonreactors. Thus there is about 10 times as much tuberculosis, both manifest and latent, among positive as among negative reactors to tuberculin, and an appreciable number of cases of tuberculosis of clinical importance would have been missed by x-raying only positive-reactors. The first group of authors state (p. 138): *"the tuberculin tests did not reveal all persons with demonstrable x-ray lesions, a few of which were manifest.* Consequently any final discussion of the amount and character of tuberculous infection . . . . should take into consideration the results of *both tuberculin tests and x-ray examinations"* (italics ours).

†During the war years of 1939 and 1940, the death rate from tuberculosis in England and Wales for the population as a whole increased 9.7 per cent over that in former years, and the highest rate of increase, 15 per cent, occurred in females between the ages of fifteen and twenty-five, a group which already had the highest rate.[31]

bearing age, tuberculosis is still first as a cause of death. The tuberculosis toll of this group accounts for 20 per cent of all deaths, twice as high a mortality as from all puerperal causes.[32] In the light of these facts, a roentgenologic case-finding method becomes an essential part of prenatal care.

SUMMARY AND CONCLUSIONS

1. The inadequacy of symptoms and physical examinations as means of discovering pulmonary tuberculosis has been discussed. An error of 90 per cent may be expected when these methods alone are used.

2. Routine chest fluoroscopy, followed by roentgenograms in all cases with definite or suspected lung pathology, is a satisfactory method of finding tuberculosis when carried out by an experienced examiner trained in fluoroscopic technique and lung pathology.

3. Application of this method to 10,968 pregnant women, unselected except for the exclusion of known tuberculosis, disclosed 110 cases of unsuspected clinically important tuberculosis, or an incidence of 1.0 per cent. Seventy-four cases, or 0.7 per cent, were shown to be active during the pregnancy.

4. The incidence of unsuspected tuberculosis has remained nearly the same for the two periods of this investigation, namely, 1.06 per cent during 1934 to 1937 and 0.96 per cent during 1937 to 1941.

5. In contrast to this, the incidence of unsuspected syphilis declined markedly, from 0.87 per cent during 1934 to 1937 to 0.30 per cent during 1937 to 1941. This decline may be attributed to the passage of the Illinois hygienic marriage law in 1937.

6. Routine chest roentgenologic examinations should rank with routine Wassermann tests as a medical necessity in pregnant women. The desirability of premarital laws relating to tuberculosis similar to those relating to syphilis has been discussed.

7. Tuberculosis in pregnant women is still an important problem, for although it has declined from first to seventh place as a cause of death in the general population, it still remains as the leading cause of death for women of the child-bearing age. The tuberculosis toll in this age-sex group accounts for 20 per cent of all deaths, twice as high a mortality as from all puerperal causes.

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PROGRESS IN MYOMECTOMY*

Surgical Measures and Diagnostic Aids Favoring Lower Morbidity and Mortality

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THE operation of myomectomy was devised a little over one hundred years ago. According to Noble,[1] 1906, the earliest operations for the removal of fibroid tumors of the uterus were myomectomies. The first deliberate removal of a fibroid tumor was performed by Amussat in 1840. Amussat's work was not fruitful, as those who imitated him in France had bad results, and the operation was soon abandoned in Paris. W. L. Atlee[1] was the next surgeon to perform a myomectomy, which was the first successful one on record. Atlee's first operation by the vaginal route was performed in 1845.

According to Bonney,[2] myomectomy, in the early experience with this operation, consisted for the most part in removing pedunculated tumors. Only later experience gave gynecologists the courage to remove fibroids

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having "shorter and shorter pedicles until at last they assayed to cope with those having none at all."

Bonney refers to W. Alexander of Liverpool, who reported in 1898, on a technique by which he had been able to remove successfully as many as twenty-five tumors from a single uterus. Alexander's paper met with hostile reception and nobody apparently referred to it until 1922 when Bonney looked up the literature on the subject.

The fuller development of myomectomy may be said to have taken place in the last three decades. Chief among its protagonists are Howard A. Kelly, C. P. Noble, and the Mayos in America and Victor Bonney in England. In 1922 William J. Mayo[3] could report upon 909 cases while Bonney in 1925 reported the results of 220 consecutive myomectomies. Both Mayos and Bonney have since reported on larger series. Counseller and Bedard[4] in 1938 reported on 523 additional cases from the Mayo Clinic while Bonney had done 403 myomectomies by 1930. Several reports dealing with 100 or more consecutive operations for uterine fibroids have been found in recent literature. But by and large there appears still to be hesitation on the part of gynecologists and more especially of general surgeons who prefer hysterectomy to myomectomy, reserving the latter for isolated cases.

The slow development of myomectomy as compared with other standard abdominal operations was stressed by Bonney as recently as 1931, when he discussed its technique. The most important objection leveled against this operation was hemorrhage, which was believed to render it more dangerous than hysterectomy.

Many gynecologists can look back upon the earliest experience with myomectomy in the period between 1905 and 1925, when hemorrhage was considerable, at times alarming, and shock was not uncommon. Too tight and massive suturing to control bleeding was followed by pressure necrosis and marked febrile and peritoneal reactions. The postoperative convalescence was further handicapped by intestinal distention and vomiting which added to the morbidity and in some instances to mortality. For these reasons many gynecologists and most general surgeons were led to prefer hysterectomy for the removal of fibroids as the more satisfactory procedure.

There is another reason which may account for the unpopularity of myomectomy. The matter of conserving genital function was apparently negligible in the early decade of this century; it was still the era of removing ovaries for the slightest pathologic indication. Credit is due Howard A. Kelly[5] and William J. Mayo for having urged the importance of conserving both reproductive and menstrual function for women in the third and fourth decades of life.

Since Mayo's recommendation, the operation of myomectomy has appeared to gain in popularity. But this has followed the tendency toward surgical conservatism in general, especially with regard to the ovaries. Perhaps to some extent the advances made in the study of different aspects of sterility and of endocrine function may account for renewed interest in myomectomy.

In many cases hysterectomy has been performed where myomectomy would have been feasible. On numerous occasions I have been able to demonstrate upon the extirpated myomatous uterus that the fibroids could have been enucleated satisfactorily, leaving the organ intact. Careful inspection and palpation of the myomatous uterus in situ can well reward surgeon and patient for the few moments spent in determining the possibility of doing the more conservative operation. The surgeon's interest in the special task and his sympathetic attitude toward conservatism are essential prerequisites to the technical problem at hand. This is undoubtedly as important in performing myomectomy as in any other plastic reconstruction of organs and tissues.

Still another reason it has seemed to me for a lessened interest in acquiring familiarity with measures designed to conserve the reproductive function in women, is the expeditious manner in which hysterectomy may be carried out in accordance with accepted technical standards. The experienced gynecologist who is especially interested in retaining the uterus will, however, go to the extreme pains, as Counseller[6] has done, of conserving menstrual function, though it becomes necessary to anastomose the body of the uterus with the lower portion of the cervix after removing part of the uterus occupied by a cervical fibroid. I have several times removed large intraligamentous fibroids and subcervical fibroids, leaving the uterus intact with conservation of menstruation and, occasionally, of reproduction.

Myomectomy is not feasible under three circumstances:

1. When the adnexa are hopelessly diseased and a plastic reconstruction of the Fallopian tubes is impossible, the ovaries being in such bad condition through chronic inflammation or endometriosis as to contraindicate partial resection.
2. When malignancy, especially carcinoma, is present.
3. When there are adenomyomas which cannot be shelled out without sacrificing too much of the myometrium.

Myomectomy may be said to be indicated chiefly in the childbearing age (1) to conserve the possibility of reproduction, and (2) to conserve menstruation.

The painful experience encountered by most gynecologists who have had to do a hysterectomy for fibroids in a young woman, particularly one who has never borne a child, will not fail to make them consider carefully the feasibility of doing a myomectomy whenever it is possible.

In general, nulliparous women under 40 years of age, who are to be operated upon for fibromyomas, may be offered the choice of a myomectomy with the proviso that it may not be possible to carry it out successfully. When no children are desired, an attempt can be made to conserve the uterus for menstruation and endocrine balance, particularly in the neuropathic patient, provided the adnexa are found to be in good condition. Formerly myomectomy was considered only in relatively

young women. There appears to be a growing tendency in all parts of the world to extend the operative indication beyond the fortieth year. The age limit has been raised by some gynecologists to 45 years.

With few exceptions, myomectomy is confined to the period of reproduction. Beyond this period of life it is infrequently encountered. Less than 5 per cent were met in 481 cases of myomectomy at Mt. Sinai Hospital in women over fifty years of age (Table I); 14 between 50 and 60, i.e., 3.9 per cent; 5 cases between 60 and 69, i.e., 1 per cent. Only 12 myomectomies were done after the menopause. The earlier in the childbearing age fibroids are encountered, the more ideal is the operation of myomectomy.

TABLE I. AGE DISTRIBUTION OF 481 MYOMECTOMIES

20-29 years	127
30-39 years	299
40-49 years	36
50-59 years	14
60-69 years	5

It will be seen from this table that 426 myomectomies were done between the twentieth and fortieth years (88.5 per cent).

Exceptionally girls under 20 may develop one or several or more fibroids. Bonney had an extraordinary case of a girl of 19 from whom he removed 92 fibroids. The chances for developing new fibroids in such case must be considerable, first because of the long period of years left to her and second, as Bonney has remarked, because the disposition to grow more fibroids must be peculiarly inherent.

Although the incidence of first pregnancies in the fifth decade is not large, it is sometimes of the greatest importance to a newly married woman of 40 or over, who, despite having fibroids, continues to menstruate and, therefore, hopes for a child.

It is noteworthy that of the 481 patients in whom myomectomy was done, 224, or 42 per cent, had never conceived and 88 patients had had one child; 39 had two children. The rest had three or more children. In the whole group the total number of children born was 362. Of those who were gravid at some time, 58 had had one miscarriage, and 24 had had two miscarriages; the rest had had from 3 to 5 miscarriages. The total number of miscarriages was 116, or one to three of pregnancies at term.

That myomas actually play a role in the production of sterility has been proved repeatedly by pregnancy which follows enucleation of the tumors. Twenty-five of the 481 patients were pregnant at the time of myomectomy in the material of the Mt. Sinai Hospital; 13 of these went on to full term.

The ovarian cycle and its secondary menstrual cycle are essential during the period of reproduction, not only for childbearing but also for health, being an important link in the chain of endocrine function.

It has been demonstrated by hormonal assays that in the normal menstrual ovulation cycle there is an increase of female sex hormone at about the time of ovulation and again a few days before the next menses. Immediately after the onset of the menses an abrupt drop regularly takes place. The ovaries, however, continue to function even when the uterus has been removed and the blood cycle is not abolished.

Malignant changes of myomas occur in from 2 to 4 per cent of cases. Examination of fragments of the fibroids by frozen section can be resorted to before closing the abdomen when one of the tumors is at all suspicious. If the pathologic diagnosis is not conclusive, hysterectomy may be deferred until more complete histologic studies have been made of the tumors or at once be carried out without waiting for the laboratory report. Should the laboratory findings determine malignancy one may resort to the use of x-ray or radium.

Sarcoma can at best only be conjectured preoperatively. During the operation it will not often be possible to recognize its presence by inspection. When opportunity has been afforded to observe the progress of the growth which is rapid, sarcoma will naturally be strongly suspected. A very fleshy tumor, showing degenerative changes, provokes suspicion of its malignant character. In such cases a frozen section can give the desired information.

Should the diagnosis of sarcoma be made positively it will then be necessary to consider its size, its removability, the patient's age, her parity, and, in case of sterility, her keenness for childbirth. In a young woman who has borne no children, one can take the risk of removing the tumors and treat them as fibroids, keeping careful watch in the future. If there should be any signs of activity or tendency to rapid growth, resort to x-ray therapy can obviate an operative intervention with complete satisfaction because sarcomatous degeneration of fibroids is entirely amenable to x-ray therapy. On the other hand, hysterectomy can be done if this should be considered preferable.

Sarcoma has been encountered five times out of 481 myomectomies in the cases at Mt. Sinai Hospital. In all 5, the tumor was relatively small and was discovered by the routine examination in the pathologic laboratory. Two were spindle-celled sarcoma and three myosarcoma. Three patients became pregnant and have shown no tendency to recurrence. In several instances frozen section showed marked cellularity without atypical mitosis. Careful follow-up in such cases is essential.

Hilliard Miller[7] has recently made a plea for myomectomy in women between 20 and 40 years. In 141 myomectomies he found microscopic sarcoma in three specimens. Greenhill[7] remarks editorially in connection with Miller's report that removal is nearly always curative without need of postoperative irradiation and that it is rare for recurrences to manifest themselves after such sarcomas.

Carcinoma may be associated with fibroids. In a series of 188 cases, Bland found carcinoma of the cervix twice and of the body eleven times. In the 481 cases of myomectomy of the present report there was not a single carcinoma. The reason for this absence is difficult to explain except in the possible peculiar immunity to cervical carcinoma enjoyed by the patients in the material from Mt. Sinai Hospital. On the other hand fundal carcinoma is by no means rare. Perhaps the uterine cavity was not entered in a sufficient number of cases to discover fundal carcinoma. Nevertheless there was not a case encountered in the follow-up.

The question of malignant disease associating with fibroids frequently comes to the foreground. Carcinoma apparently does not develop in the myoma per se. If present in the myomatous uterus, it arises from the cervix or the endometrium. When found, it demands total hysterectomy with radiotherapy or radiotherapy alone. It should never escape diagnosis, because curettage and biopsy of the cervix may be relied upon to establish its presence in suspected cases. Although not encountered in the Mt. Sinai Hospital series, uterine carcinoma has been found associated with fibroids in from 1:2 to 3:4 per cent of cases reported in the literature. It should therefore always be kept in mind.

In connection with the diagnosis of carcinoma it is possible in most cases to demonstrate its presence or absence by injecting a viscous soluble x-ray opaque solution into the uterine cavity.[8] For this purpose only 2 or 3 c.c. of the contrast medium are used, the outlines of the growth being visualized without the danger or the necessity of the fluid entering the peritoneal cavity. This method may be used as a routine preliminary step in cases where myomectomy is contemplated and carcinoma is even mildly suspected. The method may precede exploratory curettage which it may render unnecessary.

Mortality following myomectomy was appreciable in the beginning of the present century. Five per cent mortality was regarded as favorable. Higher rates were not infrequent.

The more recent statistics show considerable improvement. Counseller and Bedard[4] reported a mortality of 1.14 per cent in a series of 523 myomectomies between 1925 and 1934. Hamant,[9] in 1933, reported one death in 156 myomectomies. Hilliard Miller had one death in 141 cases. The operative mortality of myomectomy need be no greater than that of hysterectomy, i.e., between 1 and 2 per cent.

There have been 9 deaths (1.9 per cent) in a series of 481 myomectomies performed between Jan. 1, 1922, and Dec. 31, 1941, at Mt. Sinai Hospital distributed among 47 operators; 13 were members of the Attending Staff; 25 were on the Resident Staff; and 9 were general surgeons.

There were 3,696 hysterectomies done by the group of 47 operators at Mt. Sinai Hospital during the same period. The total average mortal-

ity was 2.8 per cent. My own series as a subgroup consisted of 394 hysterectomies (10.6 per cent of the total series) and 171 myomectomies (35.2 per cent) of the total number of myomectomies. There was in my personal cases a mortality of 2.35 per cent in the 394 hysterectomies and no deaths in 171 myomectomies. Recent results from myomectomy compare favorably with the best results from hysterectomy.

The associated adnexal lesions for which hysterectomy is done expose the patient to greater risk. Myomectomy is as a rule a clean procedure and as such should not entail the same hazard.

The danger of embolism in my experience does not enter into these cases to any greater extent than in the ordinary laparotomy. There was one fatal embolism in the 481 cases at Mt. Sinai Hospital.

The morbidity of all cases, using the American College of Surgeons' standard, i.e., a rise to 100.4° F. on any two days excluding the day of operation varies in different statistics. Two hundred sixty-five patients out of the 481 myomectomies had some elevation of temperature for five days; 189 had some elevation for ten days; 26 patients had some fever beyond the fourteenth day.

Although the temperature reaction is a definite index of the postoperative course following myomectomy as of any other operation, it does not have the same importance as vomiting, intestinal distress, wound healing, general discomfort or comfort, effect on the circulation and kidneys, and the duration of the hospital stay.

The duration and course of convalescence are the best practical index to the postoperative recovery. Four hundred and thirty-one of the 481 patients left the hospital within three weeks; 50 patients were hospitalized for more than three weeks. I have no comparative statistics on this point with respect to hysterectomy, but if the latter should be shown to entail a shorter period of hospitalization it would not negate the value of myomectomy for which the additional week or two is more than offset by the value of an intact uterus. My present impression is that myomectomy compares favorably with, and in many cases is followed by a greater degree of comfort to the patient, than hysterectomy.

What to tell the patient before undertaking a myomectomy is of importance. The only proper statement seems to be that one can and will do his best to conserve the uterus in attempting to remove the tumors; but that it is not possible to guarantee that myomectomy will be feasible and that hysterectomy may not prove most advisable in the end. Occasionally, after a survey of the laparotomy findings, one may consider it worth while to discuss the situation with an intelligent husband in case a general anesthetic is employed or with the patient herself in case spinal analgesia is employed. I have had occasion to resort to both these procedures.

Technical Considerations.—In reviewing early experiences with myomectomy several factors were found to account for the unfavorable results formerly encountered. (1) It was common practice to cut away a

good part of the myometrium with the fibroid. In other words the incision first made was elliptical, including a good portion of the serosa of the uterus overlying the fibroid as well as part of the muscle wall which was spread over it. The result was that, in approximating the uterine wounds, there was tension which eventually led to necrosis, separation of the uterine wound, suppuration and intestinal adhesions with intestinal obstruction more or less complete. (2) Many wounds were invariably made in order to enucleate individual fibroids. (3) The uterus was replaced into the pelvis with the uterine serosa presenting several or many wounds which provoked agglutination and adhesions. (4) Hemorrhage against which sufficient prophylaxis was not provided. (5) Inclusion of the tubal lumen in the suturing of the uterine wounds which accounted for failure to conserve reproduction.

In the days before transfusion the operation of multiple myomectomy was fraught in many instances with considerable hemorrhage leading to much lowered resistance and shock which was not combated adequately and hence the immediate outcome of the operation as well as ultimate postoperative recovery were often unsatisfactory.

Sometimes the surgeon took the precaution of having an assistant hold the broad ligaments to prevent too much bleeding. Resort to hot pads applied intermittently during the operation controlled hemorrhage to some extent.

The postoperative morbidity and mortality were so much greater than attending hysterectomy and other operations, that most gynecologists and, more especially general surgeons, abandoned myomectomy for the operation of hysterectomy where all the bleeding could be completely controlled.

The problem therefore was threefold: (1) to plan the removal of the tumors in such fashion that they can be enucleated through a minimum of incisions, sometimes one incision sufficing to enable the surgeon to remove several fibroids. (2) The incisions were preferably made on the anterior and superior surface of the uterus, sparing the posterior and posteroinferior aspects as much as possible while keeping a safe distance from the tubal insertions. (3) The incision should be linear and never elliptical, partially bisecting the fibroid so as to determine readily the subcapsular plane of cleavage. Each half of the tumor is grasped with a tenaculum, enabling easy peeling out in an avascular fashion. Blunt and sharp dissection are used. I have found a gauze sponge very handy for the enucleation. Before it is completely enucleated the two halves of the tumor are twisted, thus forming a sort of pedicle which is clamped and cut.

By careful suturing, the cavity left by the enucleated fibroid is obliterated and more or less natural configuration is conserved. Continuous and interrupted sutures may be employed. In suturing the seromuscular layers care should be given to accurate but not too tight ap-

proximation to avoid whitening of the wound edges. Necrosis leads to suppuration, adhesions and eventually intestinal obstruction. A seroserosal suture of the Cushing type is desirable, care being taken not to include the lumen of the interstitial portion of the Fallopian tubes if the latter are encroached upon by the myoma.

The tendency to excise elliptical portions of the seromuscular layers before enucleating the tumors has proved a decided disadvantage. It is better to have a loose flap which can be imbricated, affording close serosal approximation without tension. If necessary, excessive tissue can be trimmed after the nucleation and obliteration of the tumor cavity has been completed. The peripheral sutures may now be tied without undue tension. This procedure allows for wound approximation comparable to the closure of the uterine wound in a cesarean section. Through one incision it is possible to plan the removal of a number of fibroids by squeezing them through the exposed uterine wound and thus visualizing them. When this is not feasible one can locate the tumor, incise it boldly and treat it in the same way as the subserosal intramural tumor at the first attack. If pedunculated tumors are close to either pole of the incision the pedicle can be circumcised and included in the main incision. For multiple subserous tumors it is a good plan to pass a suture to one side of the pedicle cutting it off with due allowance for serosa which can be approximated by the continuation of the preliminary suture.

For securing hemostasis several methods have been employed in my series:

(1) The old method of having an assistant grasp the broad ligaments firmly whenever possible until the fibroids have been enucleated and the suture is complete; (2) clamps protected with rubber tubing are applied to the broad ligaments, utilizing ordinary Carmalt clamps or enterostomy clamps similarly protected. In many cases this was satisfactory. (3) In a number of instances broad tape or stout silk thread was passed by means of a Deschamps needle from the immediate proximity of the lateral wall of the cervix through the broad ligament on each side and tied over its upper margin or just underneath the tube, to avoid the possible cutting through of its lumen. This also was satisfactory in some cases but could not be applied in others where the tumors were large and distorted the broad ligaments or where adhesions made it unfeasible. Whenever possible the uterus may be brought out of the abdominal wound so that the peritoneal cavity can be protected against seepage and at the same time hemostasis more completely secured. (4) The last two and one-half years I have utilized an elastic rubber turniquet passed through the broad ligament from 1 to 1½ inches outside of the lateral margin of the cervix encircling the cervix on four sides. By stretching the two ends taut posteriorly and crossing them, the ligature is clamped at the constricting point. This has proved the most effective and completely hemostatic method so far devised. I have first tried out this method preliminary to hysterectomy in order to determine how much bleeding was actually occasioned when various portions of the

uterus were incised. In practically all cases where the preliminary test was made incidental to hysterectomy, complete hemostasis was demonstrated. Only when the incision was made into the proximal portion of the isthmus was slight bleeding encountered, but the uterus itself could be incised ad lib without causing any appreciable bleeding. A similar experience was met in myomectomy. The fibroids can be incised bloodlessly, enucleated, and the bed obliterated by appropriate suturing, after which the clamp is removed from the tourniquet and the latter withdrawn. The four openings made by the tourniquet on the anterior and posterior aspects of the broad ligament are then closed by fine catgut sutures which require one or two minutes.

It is a good plan in using this method not to allow the tourniquet to be applied for more than ten minutes at a time because it is theoretically possible that tissue devitalization can take place with the production of histamine which can swarm into the circulation causing possible shock. In one of my first cases from which 33 tumors were removed in this fashion, the elastic ligature was applied for some forty minutes. The patient went into shock after being returned to her bed, and was restored after several hours by intravenous infusion, ephedrine, coramine and cortate medication. There had been no bleeding to account for the shock nor was the operation so long as to consider it a factor in its production. It is quite possible that shock was produced in this case by the prolonged application of the elastic tourniquet. This accident has not been encountered in several dozen myomectomies in which the tourniquet has since been used.

P. Borras[10] of Rosario, Argentina, has reported well over 100 cases in which he made use of the elastic ligature since our discussing this procedure in 1939, but made no mention of shock. In a personal communication, Borras expressed the opinion that the shock observed by me in the case in which 33 tumors were removed was due to the length of the operation. With this opinion I do not agree as the length of the operation was one hour and twenty minutes which should not per se induce shock.

The elastic ligature has been used in a number of ways, especially in the early Porro technique. Its use as a cervical uterine vessel tourniquet appears to have been published only comparatively recently by Borras. Yet the idea may have occurred to others. William Linder of Brooklyn had occasion to use this very method some thirty-odd years ago in a case of fibroids but never published it or followed its use in other cases.*

It is not suggested that this elastic rubber tourniquet be used in all cases. It is not necessary to employ it for a simple pedunculated fibroid or for small tumors. It is especially indicated where several or more intramural fibroids of good size are to be enucleated and where bleeding can be reasonably certain and considerable. The possibility of injuring the ureter is essentially theoretical. It can absolutely be avoided by

*Personal communication.

passing the ligature through a thin avascular portion of the cervix just above the level of the uterocervical junction. Compression of the ureters if this takes place for ten to twenty minutes cannot cause ureter injury. In none of the cases in which the broad ligament cervical tourniquet was used has any injury been encountered.

Of equal importance with the prevention of hemorrhage is the protection of the uterine wounds after the fibroids have been removed. I believe that attention to this matter has saved a good many uteri and has encouraged me to perform myomectomy where I ordinarily would have considered hysterectomy and where the latter operation was advised by colleagues.

Realizing the importance of protecting the uterine wounds, in my early experience I found it serviceable to fix the omentum by fine sutures to the wound area of the uterus or by ventrofixing the uterus to the abdominal wall. Later I employed the anterior edge of the incised vesicouterine peritoneum to cover over most of the uterine wounds, thus at the same time anteverting the uterus and preventing its retrocession into the pelvis. At first the anterior uterine pouch was incised, the peritoneum freed as widely as possible and then sewed to the uppermost angle of the uterine wound. Later I found that it was not necessary to make a flap as in the low flap cesarean section but to tack the intact loose portion of the vesicouterine peritoneum on to the uterus and protect the uterine wounds horizontally. This has been later modified by the equally simple measure of sewing the loose portion of the parietal peritoneum from side to side over and above the upper limit of the uterine incision and completely extraperitonizing the uterine wound area. A portion of the posterosuperior uterine area can thus be segregated from the general peritoneal cavity.

For the low situated posterior uterine wounds, I have employed the appendices epiploicae from the sigmoid or by actually tacking with interrupted fine sutures the sigmoid serosa to the posterior uterine wall. The sigmoid being mobile does not overcome the fixation from above which anteverts the uterus so that in the end the uterus maintains a fairly normal position. When the fibroid is situated at the uterine cornu, the uterine wound may be covered over simply by taking some sutures between the round ligament and the uterine serosa as in the treatment of adnexal pedicles. Both round ligaments may be utilized if the cornual fibroids are bilateral.

In my whole series only one of the early cases had definite symptoms of subacute intestinal obstruction. The uterine wound had not been protected in the manner just described. This patient recovered, thanks to gastric and intestinal drainage and intravenous infusion. In the entire series of 481 myomectomies only one case of postoperative intestinal obstruction required a second laparotomy for the release of a kinked, adherent loop of intestine. This patient recovered.

An important item in prophylaxis of morbidity and mortality in connection with multiple myomectomy is the avoidance of routine appendectomy. It has been a long standing conviction that a quiet, i.e., normal looking appendix should not be removed at the conclusion of a myomectomy because it is so "handy."

One need only to scan the literature and review his own results after laparotomy for pelvic disorders, where an incidental appendectomy was done in order to be convinced that morbidity and mortality are occasionally produced by the appendix stump no matter what the particular technique employed. It is a good rule after performing a complicated hysteromyoplasty to inspect the appendix and to remove it only when adherent or otherwise diseased. Simple myomectomies may be more safely combined with routine appendectomy.

Ventrofixation and Ventrosuspension as a Precautionary Measure.—When the incisions have been made on the posterior aspect of the uterus, the latter has a tendency to be anchored down. In order to avoid this the uterus may be ventrofixed by separate plain catgut sutures. Suspension by the round ligaments may also be done. Ventrofixation, moreover, approximates the uterus to the abdominal wall so that if there is any oozing or infection, it may come through the abdominal wound rather than invade the free peritoneal cavity. The fixation produced by plain catgut sutures is temporary and is not likely to interfere with future pregnancies. But this procedure should be reserved for cases where it is chiefly desirable to conserve menstruation.

An idea of the frequency of tubal disease associating fibroids is given by the fact that there were 89 cases out of the 481 cases in which myomectomy was done at Mt. Sinai Hospital. For these lesions unilateral salpingo-oophorectomy was done in 60 cases and partial bilateral salpingo-oophorectomy in 2 cases; unilateral oophorectomy in 3; partial oophorectomy in 9; unilateral salpingectomy in 6 and partial salpingectomy in 2; salpingolysis and salpingostomy in 6. Appendectomy was done in 68 cases; ventrofixation or suspension in 19; hernioplasty in 2; Fothergill operation in 2; and anteroposterior colporrhaphy in 11 cases. Pregnancy was interrupted in 3.

Lipiodol as a Diagnostic Measure.—Whenever lipiodol is used for the diagnosis of submucous fibroids or to note the distortion of the uterine cavity by multiple fibroids, the injection should be made very slowly and under fluoroscopic control. As soon as the uterine cavity is filled with lipiodol and before it enters the tubes, the x-ray film can be taken. The pressure should not be raised after the tubouterine junctions have been visualized. The oil should be allowed to escape immediately after the exposure. This precaution is taken to avoid affecting the ciliated epithelium of the tubal lining and to prevent inspissation in the tubal lumen. The use of soluble visco rayopake in fractional doses is superior to the use of lipiodol, because it leaves no residue after a few minutes.

Tubal obstruction can be demonstrated so much more conveniently by uterotubal insufflation with CO_2 that I have not used radiopaque substances for this purpose in myomatous uteri.

The diagnosis of submucous fibroids may be ventured when the patient complains of profuse menses accompanied by clots and cramps. It may be the only fibroid present, enlarging the uterus symmetrically and not beyond the size of a fist. The use of the uterine sound has value in many cases. In past experience an exploratory curettage often disclosed the encroachment upon the uterine cavity, but in a certain percentage even this procedure has failed to establish the diagnosis. We have recently employed x-ray opaque contrast media for this purpose with satisfactory results.

By and large, submucous myomas have heretofore demanded hysterectomy in preference to x-ray treatment or radium therapy. But in young women neither of these radical procedures is absolutely necessary because it can be removed as safely as the ordinary fibromyoma by the vaginal or abdominal route. When solitary it can, except in virgins, be removed by opening the anterior or posterior cul-de-sac. In virgins and nulliparous women, the abdominal route is generally preferable.

Treatment of the submucous fibroid which protrudes from the external os varies with the size and amount of protrusion and the extent of the degeneration and inflammation; also as to whether it is associated with other fibroids requiring removal. If the submucous fibroid is small and protrudes from the external os, it may be treated as a simple polyp by avulsion and in an ambulatory fashion. A larger, apparently uninfected submucous fibroid filling and dilating the vagina may require incision into the remaining portion of the capsule and also removal by avulsion. If the pedicle is long and thick it may be circumcised and ligated before cutting. Sometimes the pedicle is entirely avascular, at other times it may be attended with considerable bleeding.

If bleeding is present after removing the submucous fibroid, the uterine cavity may be packed thoroughly with iodoform gauze. If no bleeding occurs packing is not necessary.

If in addition to intramural and subserous fibroids there is present an infected, degenerated large submucous myoma, it is best to remove the protruding tumor, iodize the uterine cavity and pack it with iodoform gauze which may be left in for one or two days to control bleeding and for purposes of disinfection. The rest of the fibroids may be removed at a later date after all signs of possible peritoneal irritation or inflammation have subsided. It is unwise to attempt abdominal myomectomy at the same operation unless the submucous tumor shows no signs of inflammation.

The incision for a submucous fibroid by the abdominal route is made into the uterine fundus partially bisecting the myoma and grasping each

half of the tumor with a tenaculum forceps. By careful dissection the capsule may be freed from the tumor and shelled out, leaving the endometrium intact. The latter is recognized readily by its shimmering bluish appearance and its soft character. The tumor bed is sewn up in the same way as in the case of any intramural fibroid.

Some submucous fibroids, however, are denuded of endometrium over the pole protruding into the free uterine cavity. In such cases the latter must be entered. The mucosa can then be sewn over by submucosal sutures or by sutures which approximate the mucosal edges themselves. Accidental entry into the uterine cavity is treated similarly. If the cervical canal is patulous and no preliminary curettage was done, iodoform gauze can be passed through from above into the vagina using a special gauze passer or ordinary probe. The myometrium is then sewn over in the typical fashion.

Accidental entry into the uterine cavity which can occur in enucleating fibroids that are close to the endometrium need not militate against completion of the myomectomy in favor of hysterectomy. When this accident occurs, the mucosa is sewn with fine catgut as in a cesarean operation. In the 481 cases of myomectomy at Mt. Sinai Hospital, the uterine cavity was opened 57 times. Detailed analysis of these cases showed no appreciable influence on morbidity or mortality. The uterine cavity being clean, it practically always may be opened without adding hazard to the patient. Accidental entry into the uterine cavity, however, was not necessarily due to the presence of submucous myoma.

Submucous fibroids were removed by the vaginal route in 11 cases on the gynecologic service of Mt. Sinai Hospital since 1924. In 2 cases in nulliparous women a small fundal submucous myoma was partially exposed by anterior vaginal hysterotomy and by a single tenaculum hook brought down to a point where it could be incised and shelled out.

The presence of submucous fibroids, in addition to other types, should not discourage attempts at conservative surgery. The interesting case encountered by Dr. H. N. Vineberg in this respect is instructive. In a young woman of 26 he found that he had to cut into the uterine cavity to remove a large submucous fibroid; a number of intramural and subserous fibroids had already been removed. The uterine wounds were all carefully sutured, leaving an organ which differed considerably from the normal nonfibroid-bearing uterus. This patient skipped her next period which should have appeared during her hospital stay and she was duly delivered. Despite the invasion of the uterine cavity, the young impregnated ovum continued to grow to term. As this may have been the only chance this patient had for pregnancy, the surgeon's conservative efforts were abundantly rewarded.

Multiplicity of Fibroids.—Formerly, multiple fibroids at once discouraged any attempts at enucleation. As Bonney remarks, it was

thought that the multiple enucleation would leave a uterus unfit for pregnancy and in the event of conception would be a source of danger. It is, however, surprising how often it may be possible to enucleate most if not all of the fibroids when one starts out with the express object of conserving the uterus. I have removed 33 fibroids from a young woman of 31; and Bonney reports the removal of over 100 fibroids in a single case.

Not all fibroids need to be removed. The large fibroids are always enucleated. In many cases smaller fibroids may be left in situ when their position is in neutral places and their removal might jeopardize the patient's chances for operative recovery.

Multiple enucleations should be attempted unless the technical difficulties are too great, entailing danger per se to the patient. In such cases one may be compelled to do a subtotal hysterectomy or high amputation of the uterus, preserving the menstrual function or, as is the practice in Holland, of transplanting some endometrium in the cervical stump with satisfactory results (Wijsenbeek).*

There will always be a few cases where some factor arises to prompt the surgeon to leave in one or several small fibroids although it would be preferable to remove them. An anesthetic badly tolerated by the patient or some untoward accident otherwise demanding cessation of further operating may lead the surgeon to a quick decision of concluding the operation as fast as possible. Shock is another consideration. If after removing many fibroids one or two are found on the lower posterior aspect of the uterus the removal of which may demand more time than is required for the simpler removal of fibroids more favorably situated, it is wise not to attempt it. Surgical judgment is tested by just such incidences. It is better under these circumstances to be content with an incomplete removal than with a serious postoperative result.

In Bonney's series of 403 cases the tumors removed were solitary in 166 and multiple in 237.

In 219 cases out of 481 of the Mt. Sinai Hospital series, only one myoma was enucleated. In 262 cases, from 2 to 33 fibroids were removed.

In several cases of young women, myomectomy was followed for ten or more years with normal menstruation and the birth of one or two children before symptoms suggesting new fibroids manifested themselves. The operation of myomectomy may be said in such cases to have earned its own reward. A second myomectomy is rarely done, but in properly selected cases can undoubtedly be repeated. Each case must naturally be treated accordingly. I have recently operated upon a married woman of 40 years, removing multiple fibroids six years after a previous myomectomy done elsewhere. The cervical broad ligament tourniquet made the second myomectomy possible and satisfactory.

*Verbal communication.

Recurrent fibroids should be distinguished from polypoid sarcomas which, according to Frank, were doubtless confused by older authors.

The question of recurrence is always properly asked by the patient and considered by the surgeon. Fibroids that have been removed never leave residue from which other fibroids arise. In practically all cases it is safe to say that "recurrences" consist of fibroids that were present at the time of operation which were either overlooked or actually seen but not removed for one reason or other. The new fibroids spring as a rule from seedlings that escaped the eye at the laparotomy or small fibroids which were concealed by their deeply lying sites in the walls of the uterus. In such cases, depending upon the age of the patient and other factors, a second myomectomy may be done, or resort may be had to x-ray or radium. These measures, including secondary hysterectomy should be weighed against successful pregnancies following myomectomy.

SUMMARY

Myomectomy was begun a little over one hundred years ago as a bold surgical venture for the removal of a pedunculated tumor which was erroneously believed to spring from the ovary. If there were other similar embedded tumors they were considered inoperable. The operation has gradually developed technically so that today multiple myomectomy is done as a conservative plastic operation upon the uterus with the specific object of not only removing all of the fibroids but of conserving the uterus with retention of menstruation and possible reproduction.

Three dangers attending the operation to an appreciable degree, namely, hemorrhage, postoperative morbidity, and mortality, were gradually reduced by improvements in surgical technique. Hemorrhage has been controlled by temporary constriction of the uterine vessels by the fingers of an assistant, by rubber covered clamps, and finally by use of an elastic rubber tourniquet circumscribing the cervix and constricting the uterine vessels on either side. This elastic tourniquet has made possible the bloodless removal of many fibroids which previously would have indicated hysterectomy.

The reduction of morbidity and mortality was further brought about by careful planning of the uterine incisions which were placed mostly on the anterior and superior surface of the uterus and removing as many fibroids as possible through one incision. By providing adequate peritoneal protection of the wound, covering them with vesicouterine peritoneum, anterior parietal peritoneum, sigmoid epiploica and omentum according to the requirements of the conditions met in the individual cases, intestinal agglutinations, intestinal adhesions, postoperative distress, and morbidity were further reduced. The mortality has been reduced in fairly large series of cases to 1 per cent and below, comparing favorably with the best statistics on hysterectomy.

The complete planning of myomectomy includes diagnostic measures by which to exclude or demonstrate the presence of intrauterine lesions, chiefly, retained products of conception in incomplete abortion, submucous myoma, polyps, and carcinoma. These can be diagnosed by exploratory curettage done before the myomectomy. Practically all intrauterine lesions are amenable to demonstration by means of radiopaque media injected into the uterine cavity. A viscous soluble crystalloid iodine solution has been found useful and safe and may replace diagnostic curettage. Uterine polyps may be removed by curettage and the polyp forceps, and submucous myomas may be removed by vaginal or abdominal hysterotomy at the same time as other fibroids are removed. If the operation is designed to relieve sterility the uterine incision and suture should guard against implicating the insertion of the Fallopian tubes.

Recurrences are relatively rare and arise from seedling fibroids overlooked at the time of operation or escaping inspection because of their embedded location. The choice of a second myomectomy is left in such cases to the patient, provided she is young enough and still desires children or resort may be had to hysterectomy or radiotherapy. In from 25 to 35 per cent of the cases, myomectomy has been followed by pregnancy. This would appear to justify the pains taken by the surgeon in conserving the uterus.

Myomectomy is the ideal and at present the only conservative treatment for uterine fibroids which preserves menstruation and the possibility of reproduction.

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Ballon, H. C., and Goldbloom, A.: Serious Injury to the Rectum From Improperly Administered Enemas, Canad. M. A. J. **45**: 345, 1941.

A severe injury to the rectum of a 5-year-old child caused by the improper administration of an enema is reported. In reviewing the literature, note is made of 4 cases of severe rectal injury occurring in parturient women. One was produced by an enema three days post partum and the other 3 were injuries caused by enemas given during labor.

CARL P. HUBER.

SOURCES OF ERROR IN THE DETECTION OF OVULATION*

Correlation of Vaginal Smear Studies With Urinary Pregnanediol Glucuronidate Determinations

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THE detection of ovulation in the human being constitutes one of the fundamental problems in the physiology of reproduction. For a number of years, endometrial biopsy analysis has been the only practical method available for determining whether or not ovulation had occurred in a particular cycle. The basis of this indirect method rests on the assumption that progesterone activity on the endometrium of the uterus is produced by a corpus luteum which can be formed only as a consequence of ovulation. The presence of a premenstrual proliferative endometrium, on the other hand, has been interpreted as indicative of an anovulatory cycle.

However, the assumptions necessary for utilization of this method meet with both theoretical and practical objections which detract from the usefulness of this procedure for the detection of ovulation. The most important of these objections may be listed as follows:

a. Ovulation may occur with a resultant deficient corpus luteum which may secrete amounts of progesterone insufficient to produce a secretory endometrium or the corpus luteum which is formed may be functional for a short period of time. In both cases a premenstrual proliferative endometrium might be found.

b. A corpus luteum may be formed without the liberation of an ovum.

c. The number of biopsies that can be taken in any one cycle is limited, and thus the date of ovulation cannot be determined accurately unless two biopsies are taken relatively close together and reveal first a proliferative and subsequently a secretory endometrium.

d. Clinical experience has long suggested that certain women may ovulate during or near menstruation. Recent studies substantiate these speculations.[1, 2] It is obvious that an incorrect evaluation of ovulation in such a cycle would be likely.

e. According to some investigators, progestational proliferation may be experimentally produced by steroids closely related to progesterone, such as desoxycorticosterone[3-6] and certain of the androgens.[7, 8]

f. A very practical objection to the routine use of endometrial biopsies in the study of sterility problems is the danger that this procedure might be performed during a cycle in which conception has already

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taken place. This situation has occurred to us in four instances. In two cases a missed abortion resulted while the other two patients went on to full term with no complications and normal babies were delivered.

In summing up the significance of endometrial biopsy as a method for the determination of ovulation, we may say safely that a secretory endometrium is strong evidence that ovulation has occurred, but the finding of a proliferative endometrium does not preclude the possibility of ovulation. Unquestionably, an innocuous method involving daily studies to determine the exact time of ovulation, would be highly desirable.

Within recent years, efforts have been directed toward this objective and numerous methods have been proposed. Claims have been made that ovulation is associated with, and can be diagnosed by, changes in: vaginal pH;[9] bioelectric potential;[10] rectal temperature and basal metabolic rate;[11] oxyhemoglobin determination by the Samuels cycloscope;[12] vaginal smears;[1] and urinary excretion of pregnanediol glucuronidate (P.G.), a metabolic derivative of progesterone.[13] Most of these methods rest on an insecure basis and lack direct confirmation. Two of these procedures, however, appear worthy of more careful consideration. We refer to the vaginal smear method originated by Papanicolaou[14] and extended independently by Shorr[15] and Rubenstein;[1] and the urinary pregnanediol glucuronidate method introduced by Venning and Browne.[13]

We have undertaken a critical study of these two methods with the purpose of correlating the results obtained by these procedures. In the course of this work certain difficulties in the evaluation of ovulation by these methods have arisen. The purpose of this preliminary report is to point out these possible sources of error.

PROCEDURE

These studies were made on a large series of women with varying complaints but with no demonstrable pelvic pathology. Patients were instructed in the technique of taking vaginal smears according to the requirements of Shorr[15] and Rubenstein.[1] The smears were taken by the patient and were obtained either with the suction pipette described by Papanicolaou,[14] or by means of a wire loop inserted to the posterior fornix through a speculum. Preliminary results comparing the daily smears obtained with both methods taken in the same patient revealed no significant differences. The smears were stained in accordance with the method of Shorr.[15]

Vaginal smears were evaluated on the following basis: Analysis of estrogenic activity was obtained, using the criteria described by Rubenstein and Duncan.[17] Smears consisting of round cells with relatively large vesicular nuclei (basal or atrophy cells) were assumed to indicate zero estrogen production, while smears consisting of cells with agranular cytoplasm and small pyknotic or fragmented nuclei were assumed to represent maximal estrogen response. Intermediate smears were assigned intermediate values following the scheme of Rubenstein and

Duncan. It has been found that the technique of evaluating human vaginal smears for estrogenic activity on this semiquantitative basis roughly parallels the assay of urinary estrogen excretion.[17] Luteal activity was evaluated both by the degree of desquamation observed in the smear (as evidenced by the folding and aggregation of the epithelial cells) and by the inhibition of cornification due to estrogen. These reactions appear to be the effects of progesterone on the vaginal smear picture.[1, 18] The arbitrary criteria for evaluation of the degree of desquamation used in these studies were as follows:

0 Desq.----Aggregation and folding absent.
1-plus Desq.----Aggregation absent, but many cells with folded edges.
2-plus Desq.----Aggregation absent, most cells edges are folded.
3-plus Desq.----Aggregation definite, many cells are folded without being aggregated.
4-plus Desq.----Aggregation of most folded cells.

Fig. 1.—A postovulatory smear (×470), illustrating marked folding of the cell edges.

Figs. 1, 2, 3, and 4 are photomicrographs of vaginal smears illustrating varying degrees of cell cornification and desquamation. The degree of desquamation was correlated with the inhibition of cornification, the composite picture representing roughly progesterone activity. Ovulation, on this basis, was diagnosed by a sharp increase in desquamation index, with a simultaneous decrease from high levels of the cornification index. The evaluation of the degree of cornification, by examination of cytoplasmic staining, using Shorr's differential staining method,[16] cannot always be relied upon, in our experience. Although highly cornified

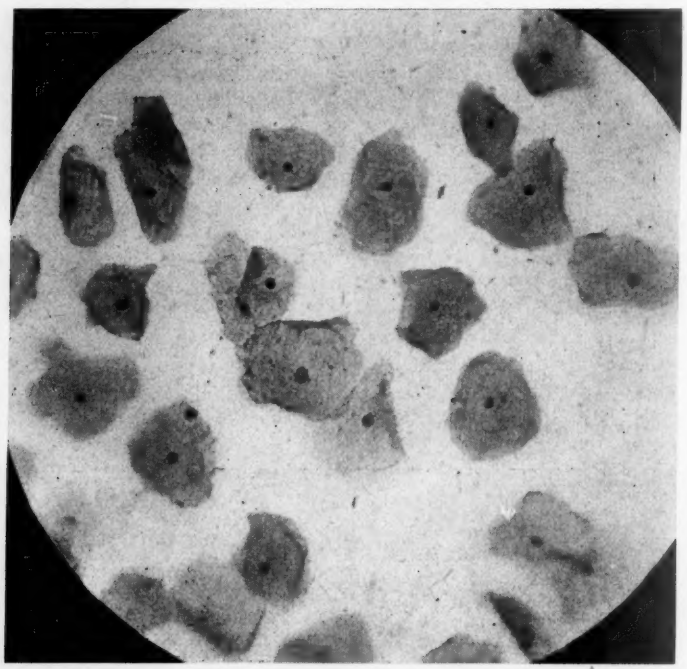

Fig. 2.—A preovulatory smear (×470), illustrating zero aggregation and minimal folding of the cell edges.

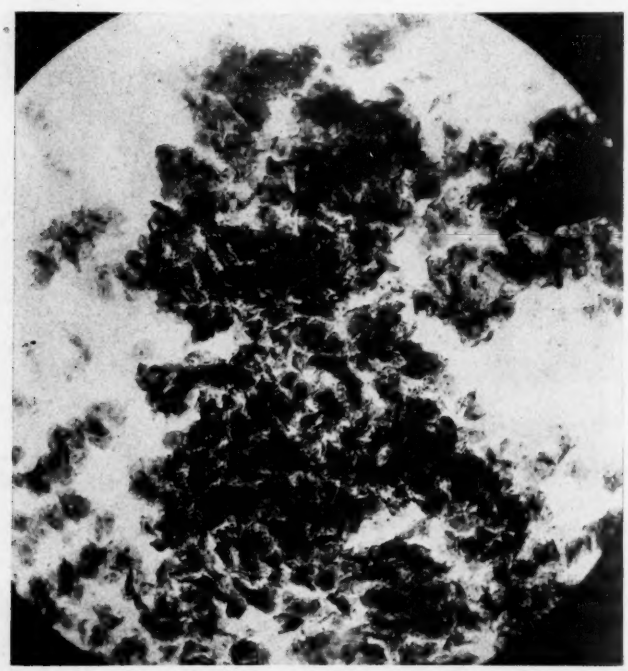

Fig. 3.—A low-power photomicrograph (×100) of Fig. 1, illustrating marked cell aggregation in a postovulatory vaginal smear.

cells usually stain red, and less cornified cells stain green, it has been possible to demonstrate green-staining cells with highly pyknotic nuclei, and red-staining cells with large vesicular nuclei. Urinary pregnanediol glucuronidate (P. G.) was determined by the modified method of Venning.[19] The figures are uncorrected for reasons that will be made clear in the body of this paper. The urines were collected over twenty-four-hour periods. In order to prevent hydrolysis of the pregnanediol complex during collection and before laboratory work-up, the following procedure was adopted: the patients were instructed to collect urines in bottles containing 200 c.c. of butyl alcohol; to shake the collection bottle after each addition of each sample; to keep the urine bottle refrigerated;

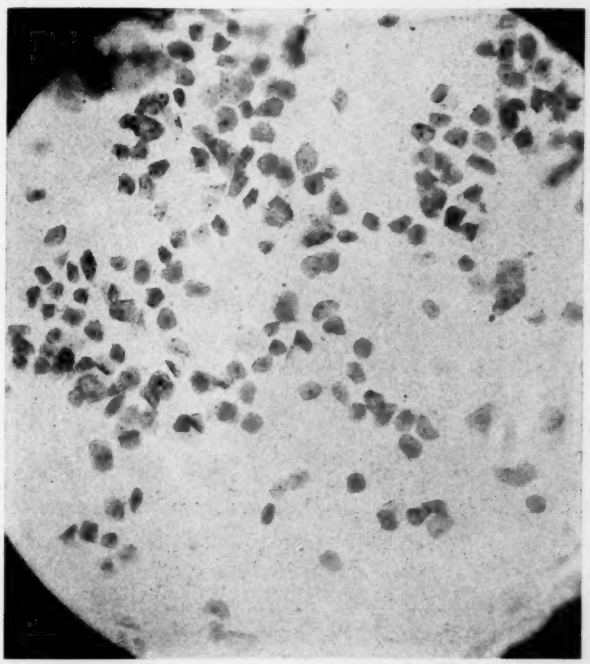

Fig. 4.—A low-power photomicrograph (×100) of Fig. 2, illustrating absence of cell aggregation in a preovulatory vaginal smear.

and finally to bring the urine to the laboratory immediately after the collection period. This procedure was adopted on the premise that extraction of the pregnanediol complex by the butyl alcohol already in the bottle would inhibit bacterial or enzymatic hydrolysis of the complex. Unpublished experiments indicate that pregnanediol glucuronidate is relatively stable under these conditions.

DISCUSSION OF RESULTS

First attempts to analyze and correlate our vaginal smear and urinary pregnanediol studies were met with considerable difficulty and confusion which almost precipitated a condemnation of the value of both methods. However, continued efforts clarified our results and justified

a more favorable interpretation. On the supposition that the specific reaction of the vaginal mucosa to the onset of progesterone activity is folding and aggregation, associated with inhibition of estrogen cornification, one should expect a curve of ovarian function similar to that illustrated in Fig. 5. It will be seen that the degree of cornification rises steadily to a high peak and then sharply declines. Associated with this abrupt drop in cornification, a sharp rise in desquamation index from zero or near zero levels is simultaneously seen. This point represents ovulation as diagnosed by the vaginal smear technique. The absence of ovulation, by this method, may be illustrated by Fig. 6. It is apparent that the practically straight lines obtained for desquamation and cornification indicate that progesterone in amounts sufficient to affect the vagina has not been liberated. In our series, however, it has been possible to secure very few cases which show the type of curve illustrated in Fig. 5. More representative of typical cycles encountered are those illustrated in Figs. 7 and 8. Here distinct evidence of desquamation may be present at any stage of the cycle, bordering at levels, indistinguishable from progesterone effects. It is apparent, however, that, when the inhibition of the cornification index is considered simultaneously, it is possible to distinguish between a true and a false progesterone response. Thus, in Fig. 7, the desquamation peak at Day 5 is clearly not ovulation, since the cornification index did not simultaneously fall with the rise in desquamation nor does the desquamation index remain high.

These artifact peaks of desquamation appear in a large percentage of the cycles studied, but need not be considered as serious objections to the smear method, since by comparing the desquamation index with the cornification index a check is furnished for the evaluation of progesterone activity. However, it is obvious that the analysis of a single or an incomplete group of vaginal smears to determine whether or not the patient has ovulated is impossible. No final explanation at the moment can be advanced for the artifact desquamations. Coitus is not the causative factor, since in numerous instances where coitus had taken place the night before, desquamation in the vaginal smear was not evident. Furthermore, the desquamation artifacts do not appear to be related to any single method of taking the smears.

Another confusing point was encountered in studying the vaginal smears of several patients. Rubenstein[20] has observed in a patient with a persistently high estrogen level, produced by implantation of estrogenic pellets, that the vaginal smear picture may change abruptly from a high degree of cornification without desquamation to one wherein significant desquamation appears, without the occurrence of ovulation. He believes that cornification is primarily a degenerative process produced by estrogen and, even in the absence of progesterone, may even-

tually terminate in a desquamation. He concludes that this desquamation is just an advanced step in the degenerative process, which does not occur under normal conditions with a normal estrogen level. Fig. 9 is a chart of the vaginal smears taken from a patient who is a sterility

Fig. 5. Fig. 6.

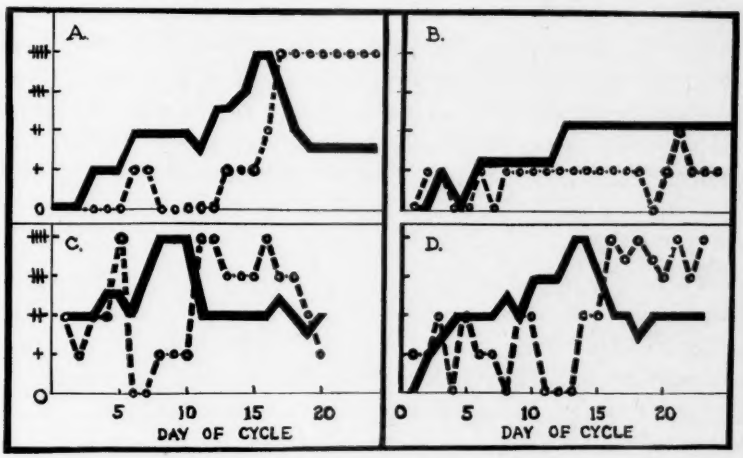

Fig. 7. Fig. 8.

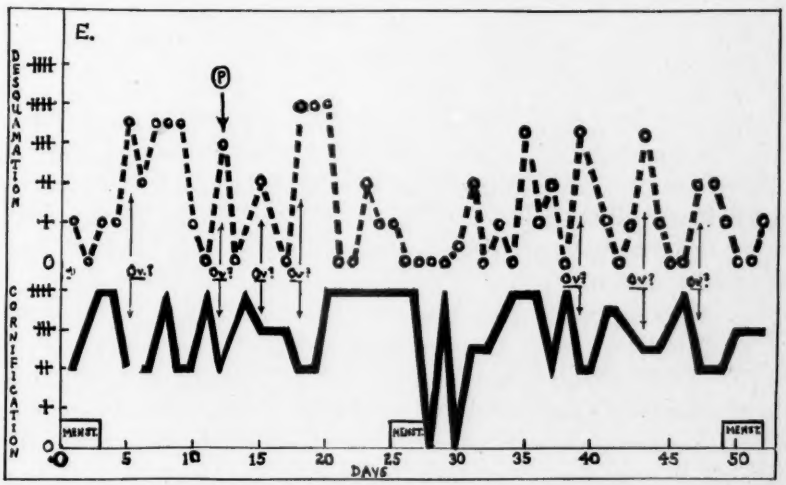

Fig. 9.

Figs. 5, 6, 7, 8, and 9.—Illustrating graphically the daily cornification and desquamation changes in 5 different patients. Cornification is represented by the solid line ———, while desquamation is shown by the broken line - - - - -.

problem of many years and is an excellent illustration of this observation made by Rubenstein. It will be seen that in the two cycles illustrated, numerous peaks of desquamation occur which might be diagnosed as the result of ovulation. The curve, however, departs from the usual

sequence, in that each period of desquamation is transient. Furthermore, there exists a persistently high degree of cornification, broken in most instances only when accompanied by the rise of the desquamatory reaction. The vaginal smear pictures of several other cases of hyperestronism under our observation demonstrated the same qualitative cyclic changes seen in Fig. 9.

Although the occurrence of more than one ovulation per cycle has been suggested by some investigators, the presumed occurrence of three or four ovulations in one cycle seems unlikely. In the case illustrated by Fig. 9, urinary pregnanediol glucuronidate was absent and a proliferative endometrium was found at a time when one of the desquamation peaks occurred, which further precludes the possibility of the occurrence of ovulation.

It has been clearly recognized that the excretion of pregnanediol glucuronidate in the nonpregnant woman depends, not only upon the secretion of progesterone by the ovary, but also upon endometrial, hepatic, and renal factors.[21] That progesterone need not necessarily be metabolized through the pregnanediol-P.G. route has been adequately demonstrated in primates and in common laboratory animals.[22, 23] Presumably this alternative pathway of progesterone metabolism is operative in human beings as well, since the recovery of parenterally administered progesterone as urinary pregnanediol glucuronidate may vary from 0 to 70 per cent.[24] In this laboratory, we have confirmed the finding that progesterone is not quantitatively converted to pregnanediol glucuronidate in women. With the participation of extraovarian factors in the metabolism of progesterone established, it is clear that quantitative evaluation of luteal activity is not obtainable by pregnanediol glucuronidate estimation in the absence of quantitative information regarding the efficiency of all factors which take part in the excretion of pregnanediol glucuronidate. Furthermore, the presence or absence of urinary pregnanediol glucuronidate may not serve as a qualitative test for luteal activity, since it is possible to obtain zero values for pregnanediol glucuronidate in the presence of circulating progesterone. Recognizing these difficulties, it is still possible to utilize pregnanediol glucuronidate determination for useful information regarding luteal activity. The presence of urinary pregnanediol glucuronidate may be taken as strong suggestive evidence for functional lutein tissue and the quantity of pregnanediol glucuronidate excreted represents a minimal estimate of the amount of metabolized progesterone. Using this reasoning as our basis for interpreting the significance of pregnanediol glucuronidate determinations we have correlated vaginal smears with urinary excretions of pregnanediol glucuronidate. One should expect that the presence of luteal activity diagnosed by the smear technique should in most cases be accompanied by a simultaneous excretion of pregnanediol glucuronidate. If a vaginal smear indicates luteal activity,

the absence of pregnanediol glucuronidate in urine collected at the same time, does not necessarily indict the vaginal smear technique, since the result might be conceivably explained as a consequence of an altered metabolism of progesterone. The vaginal smear technique, however, should be positive for luteal activity when the urine shows pregnanediol glucuronidate (neglecting adrenocortical tumors and the like).

Table I illustrates our results on Case S. R. Here it will be seen that definite amounts of a material of solubility properties similar to pregnanediol glucuronidate regularly appeared in the urine, although no evidence of luteal activity was found in the vaginal smears. Attempts to obtain melting point determinations on this material failed, although it may be emphasized here that this pregnanediol glucuronidate-like material could be obtained after three precipitations from water with

TABLE I. COMPARISON BETWEEN GRAVIMETRIC AND CHEMICAL REDUCTION METHOD FOR ESTIMATION OF PREGNANEDIOL GLUCURONIDATE (CASE S. P.)

DATE	DAY OF CYCLE (ONSET OF MENST. =1)	PREGNANEDIOL GLUCURONIDATE MG./24 HR.			VAGINAL SMEAR	
		GRAV.	CHEM.	% IMPURITY	CORN.	DESQ.
8/17/41	17	0	–	–	+	+
8/18/41	18	–	–	–	+	+
8/19/41	19	1.8	–	–	+	+
8/20/41	20	5.2	–	–	+	++
8/21/41	21	2.0	–	–	+	+
8/22/41	22	1.6	–	–	++	++
8/23/41	23	4.8	–	–	+	+
8/24/41	24	2.8	–	–	++	+
8/25/41	25	3.2	–	–	+	+
11/ 6/41	17	1.6	0	100	+	0
11/ 7/41	18	3.0	0.2	93	+	0
11/ 8/41	19	3.6	0	100	++	+
11/ 9/41	20	–	–	–	++	++
11/10/41	21	1.6	0	100	++	+
11/11/41	22	2.0	0	100	++	+
11/12/41	23	–	–	–	–	–
11/13/41	24	4.0	0	100	++	0

acetone and on macroscopic examination appeared indistinguishable from small amounts of pure amorphous pregnanediol glucuronidate. To check quantitatively the purity of this material isolated by the method of Venning,[19] a chemical method was devised in this laboratory wherein pregnanediol glucuronidate is determined by the estimation of copper reducing activity obtained after acid hydrolysis of the pregnanediol glucuronidate sample.[25]

With the development of a method to check the purity of pregnanediol glucuronidate isolated from urine, simultaneous smears and pregnanediol glucuronidate determinations on patient S. R. were repeated two months later. These data are also illustrated in Table I. It will be seen once again that definite amounts of a pregnanediol glucuronidate-like material were obtained regularly in the absence of luteal activity as diagnosed by vaginal smear. However, this material regularly failed to give the chemical test for pregnanediol glucuronidate. It, therefore, appears that this material was not pregnanediol glucuronidate, but some im-

purity present in the urine of the patient, and the vaginal smear interpretation was correct.

Table II illustrates data on Case J. M., part of whose smear history appears in Fig. 9. In the section on vaginal smears reasons were advanced as proof that the smear pattern indicated no luteal activity. Here again, definite amounts of this pregnanediol glucuronidate-like material were present in the urine, which by chemical analysis proved not to be pregnanediol glucuronidate, and therefore confirms our analysis of the smear. These data clearly indicate the necessity for the independent determination of the purity of small amounts of pregnanediol glucuronidate by means other than solubility properties. This may be accomplished by the method developed in this laboratory or by the method recently reported by Allen and Viergiver.[26]

TABLE II. COMPARISON BETWEEN GRAVIMETRIC AND CHEMICAL REDUCTION METHODS FOR ESTIMATION OF PREGNANEDIOL GLUCURONIDATE (CASE J. M.)

DATE	DAY OF CYCLE (ONSET OF MENST. = 1)	PREGNANEDIOL GLUCURONIDATE MG./24 HR.			VAGINAL SMEAR	
		GRAV.	CHEM.	% IMPURITY	CORN.	DESQ.
10/11/41	5	2.4	Total		0	+
10/12/41	6	2.7	13.9 mg.		++	+++
10/13/41	7	2.2	tested	96	+++	0
10/14/41	8	2.0	= 0.5		+++	+
10/15/41	9	2.5	mg.		++++	0
10/16/41	10	0.5			++++	+++
10/17/41	11	0.8			++++	+
10/18/41	12	0.8			++	+++
10/19/41	13	0.4	–	–	++++	0
10/20/41	14	0.3	–	–	++	+++
10/21/41	15	1.3	–	–	++	+
10/22/41	16	6.7	0	100	+++	+
10/23/41	17	1.5	0	100	++++	0
10/24/41	18	1.5	0	100	+++	+
10/25/41	19	1.5	0	100	++	++
10/26/41	20	0.2	–	–	++	++
10/27/41	21	6.0	0.9	85	+++	0

CONCLUSIONS

1. The evaluation of ovarian function by the vaginal smear method is complicated by numerous factors.

2. In most cases these factors may be properly interpreted by taking daily vaginal smears throughout an entire cycle.

3. Artifact peaks of desquamation frequently occur without a corresponding abrupt drop in cornification and do not signify ovulation.

4. Persistently high levels of estrogen may induce a desquamation similar to that produced by progesterone during the luteal phase of the cycle.

5. The supposition that the modifications reported by Venning for pregnanediol glucuronidate determination eliminates most of the impurities in the final product can no longer be considered tenable.

6. A new method for the quantitative determination of pregnanediol glucuronidate based upon the copper reducing activity of the glucuronic

acid obtained after acid hydrolysis is referred to and offered as a means of eliminating the source of error experienced with the method of Venning.[25]

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ELECTROMETRIC TIMING OF HUMAN OVULATION*

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INVESTIGATORS have long sought an adequate method for determining with certainty the time of ovulation in animals and in man. The usual methods of mating at selected times and the examination of the generative tract at laparotomy have given us a good deal of valuable information. In man these procedures have been time-consuming and not altogether satisfactory, hence the report by Burr, Hill and Allen[4] that ovulation in the rabbit was accompanied by significant modifications of an electrical pattern in the intact animal, offered a new procedure fraught with many possibilities. The findings were confirmed by Reboul, Friedgood and Davis[7] and extended by Altman.[1] Subsequently Burr, Musselman, Barton and Kelley[5] reported an electrometric change in the

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human being with confirmation at laparotomy. In this instance a recently ruptured follicle was observed and a portion of the ovary containing it was removed and studied microscopically. Rock, Reboul and Wiggers[8] extended these findings to a larger group and confirmed the experiment, although there were some discrepancies.

The consequences of this new approach are sufficiently important to require rigorous validation of the procedure, under a wide variety of conditions, especially since Rock[9] has recently reversed his original stand. Boling and others[2] have applied the technique to a very complete study of the entire estrous cycle in the albino rat and have shown, among other things, a clear-cut and significant alteration in the electrical pattern from the inception of heat to its termination. Moreover, Langman and Burr[6] reported characteristic electrical changes in uterine activity throughout the menstrual cycle in women. In continuation of these studies, an improved and somewhat simplified technique has been developed which makes it possible to record the changes in voltage gradient which exist between the human cervix uteri and some indifferent point on the surface of the body, such as the ankle.

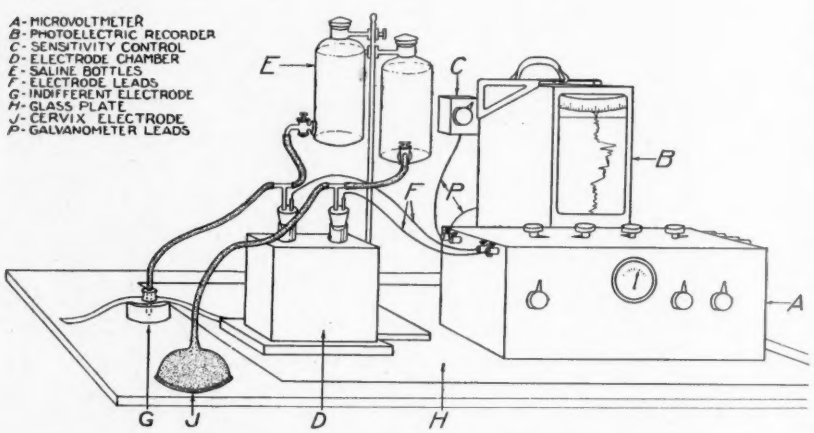

Fig. 1.—Diagrammatic sketch of apparatus.

PRESENT TECHNIQUE

The apparatus used in the procedure was a Burr-Lane-Nims DC microvoltmeter with a General Electric photoelectric recorder as a recording galvanometer (Fig. 1). The paper speed was one inch in five minutes and its sensitivity one millivolt per division. The zero baseline was in the center of the chart. Deflections of the pen to the right indicated positive polarity of the input lead to the grid of the microvoltmeter; deflections to the left, negative polarity of this lead. Contact of the microvoltmeter with the patient was made by a pair of nonpolarizable reversible silver-silver chloride electrodes immersed in physiologic salt solution. From the chambers containing these electrodes, rubber tubes were led to the patient. The one from the ground electrode terminated in a sponge rubber disc which could be strapped to the ankle. This

constituted the reference or cold electrode and its exact location on the surface of the body did not seem to be important. The ankle was chosen for convenience. The other electrode chamber was connected to the patient by means of a rubber tube, the outer end of which was cemented into the dome of a thin rubber cervical diaphragm. The cavity of the diaphragm was packed with cotton saturated with normal salt solution and was readily placed over the cervix. Both tubes were filled with saline, taking care to see that there were no bubbles of air in the lumen of the tubes or between the tubes and the surfaces of the body. In practice, the patient lay comfortably on an examining table for periods varying in time from fifteen minutes to more than an hour. No discomfort or pain was encountered at any time. It should be noted that this technique made it possible to record electrical changes in the intact organism. Hence, at all times, there was a minimal disturbance in normal physiologic processes. The use of silver-silver chloride electrodes gave assurance of a faithful record of true changes of potential difference without the artifacts of contact potential, such as are encountered when metal is brought directly into contact with body surfaces. In practice, these electrodes are stable and introduce no artificial e.m.f.'s in to the external circuit. While the microvoltmeter responds adequately to voltage changes at wide differences in frequencies, the recording galvanometer used imposes certain limitations on the records. The period of the galvanometer used is approximately three seconds. As a result, it did not respond readily to relatively rapid changes, such as accompany the heart, nerves, or striated muscle. Fortunately, however, nonstriated muscle contractions produce electrical changes of much lower frequency. Faithful records, therefore, could be obtained.

The cases were selected from the patients of a gynecologic practice and the studies were carried out in the office. The procedure was employed as a means of improving on the techniques previously used (Langman and Burr[6]) in an electrical study of uterine mobility during the menstrual cycle. While interesting data on this point were obtained, it was overshadowed by an unexpected finding, which it is the purpose of this report to present.

ANALYSES AND DISCUSSIONS

Approximately 150 records have been taken from 7 women on the majority of the days of the menstrual cycle. The studies showed that most commonly throughout the menstrual cycle the cervix was positive to the ankle from 5 to 25 mv. In 9 of the 14 cycles studied, the cervix became negative, an equivalent amount on at least one day of each cycle. In four of these, the cervix remained negative for two days. The days of the cycle on which the negativity appeared were the third, sixth, seventh, eighth, thirteenth, fourteenth, eighteenth, or twenty-first. In five cycles either no negative shift occurred or it was equivocal. The general distribution of these results is shown in Fig. 2. It will be noted that there are many gaps in each cycle, due to the necessary exigencies of an office practice. In a number of instances the recorded potential difference was so near the baseline that it was called equivocal and is marked on the chart with a question mark.

In Patients 1, 2, and 3, the first ones studied, various techniques for the timing of ovulation were employed, in addition to the electrometric procedure. Five artificial inseminations were carried out at the time when ovulation was believed to have occurred. It should be noted that in these patients the assumed time of ovulation did not correspond exactly to the day of the negative shift of the cervix. In Records 1 and 5, however, the correspondence was close. Nevertheless, in none of these patients did pregnancy supervene. There are several explanations for the failures other than the absence of exact correspondence of insemination and negative shift, for the previous matings in these patients had all been sterile.

In Patient 4, the negative shift of the cervix occurred on the thirteenth and on the fourteenth day and was accompanied by intermenstrual pain. There is some evidence in the literature which suggests that intermenstrual pain may be associated with follicular rupture. The second

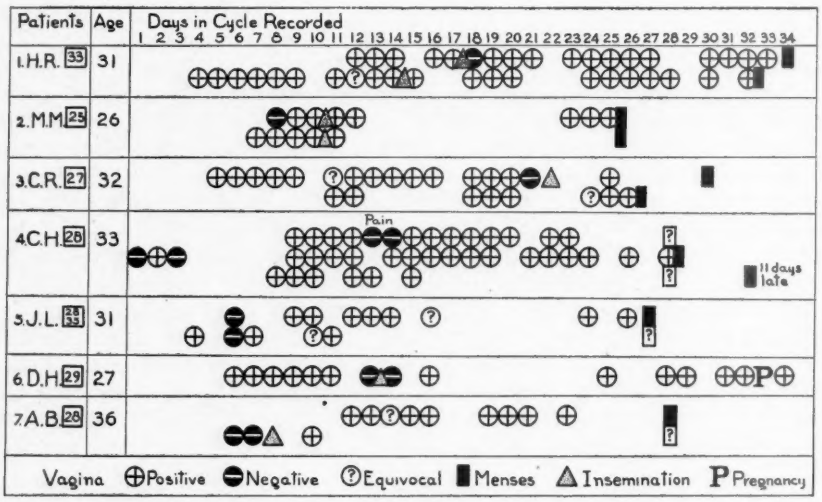

Fig. 2.—A chart of the events on successive days of the menstrual cycle.

cycle recorded in this patient showed an anomaly which is hard to explain. The cervix was negative on the first and third days of menses and no other negative records were obtained for the rest of that cycle. If the negativity of the cervix occurs at the time of ovulation and at no other time in the cycle, then this record would strengthen the view that ovulation may occur at any time in the cycle, even during menstruation.

Patient 6 deserves special attention. On the thirteenth day of the cycle, the cervix was recorded as 8 mv. negative, and on the fourteenth day this was increased to 16 mv. negative. At the end of the recording, the patient was artificially inseminated with donor sperm. As is indicated on the chart, the patient was studied occasionally from then until the twenty-ninth day of the cycle, or fifteen days after the insemination. On that day there appeared on the record a series of repeated rather abrupt decreases in the potential difference. The magnitude was 4 mv. and the frequency 8 mv. for each five-minute period (Fig. 3, *C*). These were surprisingly regular and appeared throughout the period of record-

ing. Two days later the records showed the same kind of phenomena but by the thirty-second day they disappeared. At this time the breasts became tender and the patient gave subjective evidence of pregnancy. This was confirmed by the Aschheim-Zondek test and by subsequent history (Fig. 3, *A, B, C*).

The situation in this particular patient was important because, although the patient had been married for several years, mating had been infertile. On examination this was shown to be due to azoospermia. Artificial insemination with donor sperm was resorted to on this one occasion only, in order to produce the desired pregnancy. The circumstances, therefore, acted as a very adequate control for the experiment. The fact that artificial insemination was successful suggests that the negative shift occurred at the time of ovulation, as it does in the albino rat.

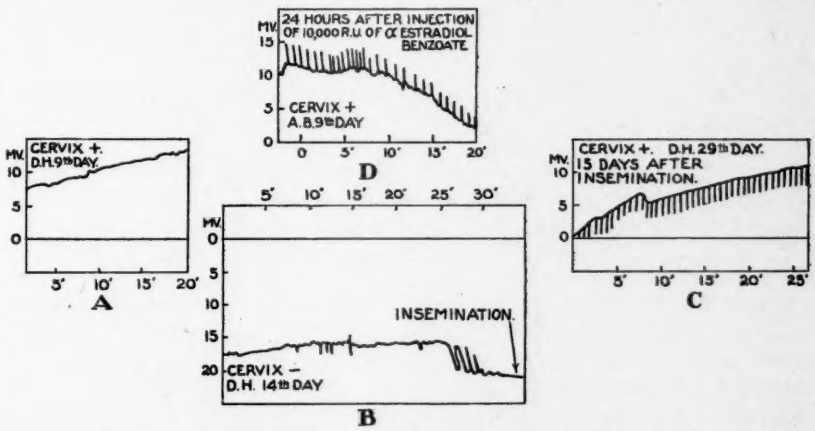

Fig. 3.—Tracings of photoelectric recordings. *A*, The ninth day of D. H. showing cervix positive. *B*, Fourteenth day of same patient showing cervix negative. *C*, Fifteenth day after insemination showing electrical activity of the cervix. *D*, Ninth day of A. B. showing electrical activity of the cervix following hormone injection.

It is noteworthy that the regular and rhythmic changes in electrical potentials described above appeared on the day when the normal menses would have occurred. The character of these changes is interesting, because they are very similar to the kind of phenomena which have been recorded in the generative tract of the albino rat during estrus. Boling has shown that these rhythmic phenomena can be induced in spayed animals by the administration of hormones. Moreover, it is generally believed that some two weeks after fertilization there is a sharp rise in the hormone level in the circulating body fluids. The evidence here presented indicates the probability that the impact of chemical agents on the generative tract produced significant changes in the electrical pattern.

Since the general muscular activity of the uterus, as reflected in changing potentials, is an important element in the physiology of the generative tract, it should be noted that all the electrical records showed a higher level of activity as early as the sixth and as late as the twenty-first day of the cycle. This fits in very well with previous findings. An additional interesting observation was that on the fourth or fifth days prior to the onset of a succeeding menses, the positivity of the cervix increased

to as much as 30 or 35 mv. and usually remained there until the actual onset of bleeding. With the onset of the flow, the voltage difference dropped to more nearly the normal 15 mv.

The history of Patient 7 (A. B.) is also of considerable interest. Although apparently a healthy young woman, with a regular twenty-eight-day cycle, and married for several years, mating had been infertile. On examination it was found that the uterus was considerably smaller than usual, approaching the infantile type. However, a number of records were taken as is shown in Fig. 2, and a negative shift appeared on the sixth and seventh days of the second cycle. Immediately following this, artificial insemination, using husband's sperm, was carried out. Twenty-one days later, when menses would have normally appeared, none occurred. However, menses did appear eleven days later. On the day before the onset of menses, the patient, as an air raid warden, had found it necessary to run up and down stairs frequently. It is not impossible, therefore, that fertilization might have occurred but with subsequent early abortion.

In an attempt to build up the uterine mechanism in the subsequent cycle, estradiol benzoate (10,000 R.U.) was administered on the eighth day. Twenty-four hours later the record shown in Fig. 3, *D* was obtained. This characteristic record is almost identical with that obtained from Patient 6 (D. H.), fifteen days after successful insemination. In both instances the records are very similar to those obtained during the period of heat in the albino rat (Boling and others[3]). Twenty-four hours later the same phenomenon was observed although the magnitude of the rhythmic changes was reduced and the frequency increased. On this, the tenth day, the patient was given another injection of the same amount and again on the thirteenth day. Following the last injection the rhythmical changes were present but much reduced in frequency and amplitude. Two cycles later, estradiol benzoate (4,000 R.U.) was given on the third day of the cycle. For the succeeding four or five days, there were moderate signs of uterine activity and on the ninth day a second injection of estradiol was given. Twenty-four hours later the cervix was negative and showed rhythmical changes of low magnitude but relatively high frequency. Artificial insemination with husband's sperm was carried out and frequent records taken up to the eighteenth day. At the time when subsequent menses were due, the patient gave subjective signs of pregnancy with swelling and tenderness of the breasts. An Aschheim-Zondek test, however, made a few days later, was negative and eventually menses appeared nine days late. It is possible that here again fertilization occurred with subsequent early abortion. The apparent absence of correlation between negative shift of the cervix and ovulation is important for it indicates that there is still a good deal to be learned about electrical phenomena associated with the physiology of the generative tract. Many more carefully controlled studies must be carried out before the final answer can be discovered.

SUMMARY AND CONCLUSIONS

The implications of the findings of this study are of considerable interest. There are obviously a good many variables involved in the physiology of the generative tract. This is also true of the single event of ovulation. The fact that it was possible to get at least one positive correlation makes it worthwhile to extend these studies to as many pa-

tients as is possible. The number of volunteer patients in an office practice is necessarily limited, so that it is desirable that the technique be employed as widely as possible. Attention, however, must be called to the fact that while the procedure is relatively simple, certain safeguards against artifacts must be employed. It should be noted that the hot lead goes to the cervix and not to the wall of the vagina. That this is important is suggested by some findings on the electrophysiology of the generative tract in the monkey where there is a very sharp gradient between the vagina and the os, with a polar reversal. Unsuspected grounds on the patient are a possible source of error. Air bubbles in the leads to the electrodes are another. Interference from other electrical devices is occasionally met with but can usually be recognized without difficulty in the photoelectrical record. The procedure is simple enough, however, so that the studies are being currently continued.

A second aspect of the findings is the pronounced effect of the injection of a hormone upon the electrical record. This corroborates in the human experimental data derived from the albino rat. They suggest the possibility of studying the effect of a variety of hormones upon generative physiology. The technique has the advantage of being employed on the intact organism, interfering little with the normal physiology. It is not impossible, therefore, that it can be utilized as an effective adjunct to other procedures in the study of endocrine physiology. This report is presented not as a final exposition but in the hope that it will stimulate others to extend these studies.

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ADDENDUM

We wish to report observations completed on two additional women since submitting the original manuscript for publication. They substantiate our previous findings and in the case of Patient L. B., add one more positive correlation with ovulation time to our series.

Patient 8.—M. J., aged 34 years, had a history of sterility for two and one-half years; menstrual cycle for the past year had been regular, thirty-one to thirty-two days. On the eighteenth day of the cycle the cervix was recorded as 5 to 15 mv. negative, having previously been posi-

tive. The patient was artificially inseminated on this day with husband's sperm. She was studied subsequently, and on the nineteenth day, the cervix was only 2 mv. negative. The twentieth day showed a marked positive shift of 15 mv. potential difference, similar to the findings prior to the eighteenth day. On the thirty-first day there appeared on the record a series of repeated abrupt decreases in potential difference. These are interesting and of possible significance, because they are similar to the phenomena recorded on the twenty-ninth day of the cycle in Patient 6, previously reported, in whom pregnancy was subsequently confirmed. On the thirty-second day and daily thereafter up to, and including, the forty-first day, recordings were similar to those corresponding days in Patient 6. At this time the breasts became sensitive and tender and the patient experienced subjective evidence of pregnancy. On the forty-fifth day, fourteen days later than the usual time, patient began to bleed. It is possible that here, as in Patient 7, fertilization occurred with subsequent early abortion.

PATIENT 9.—L. B., aged 33 years, menstrual cycle thirty to thirty-two days. Infertile mating for past several years. Ten artificial inseminations, using the husband's sperm and donor sperm, had been unsuccessful. These inseminations were performed at an estimated ovulation time and at an ovulation time determined with various other techniques.

An electrometric study was begun because of the repeated failures to impregnate this patient. A negative shift was observed on the fifteenth day of the menstrual cycle in two successive cycles recorded. Artifical insemination using donor sperm was carried out on the fifteenth day of the cycle after the recording of a negative shift in potential. Following the first insemination, normal menses ensued on the thirty-second day of that cycle. When the negative shift occurred on the fifteenth day of the following month, artificial insemination with donor sperm was repeated and subsequent menses did not appear. Pregnancy was confirmed by the Aschheim-Zondek test and subsequent history. The fact that artificial insemination was successful again suggests that the negative shift occurred at the time of ovulation. The circumstances in this case can be considered as a very adequate control for the experiment.

Jackson, W. F.: Some Observations on Maternal Welfare, Canad. M. A. J. 45: 137, 1941.

From a questionnaire study of 10,600 births in Manitoba in 1939 and 1940, it was concluded that only 25 per cent of the patients received adequate prenatal care. For this purpose adequate care was defined as 5 or more prenatal visits. If based on the actual investigation done by the physician during these visits, only 17 per cent received adequate care. For example, only 714 of 2,636 cases had a study of blood serology. The maternal death rate in the group with adequate care was 3.8 per 1,000 live births as compared with 4.6 in the remainder. The prenatal and neonatal mortality rates were 36.0 and 44.0 in the two groups.

CARL P. HUBER.

PROSTIGMINE METHYLSULFATE AND DELAYED MENSTRUATION

Evaluation of Prostigmine as a Test for Pregnancy

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RECENT studies (Hechter, Lev, and Soskin;[1] Soskin, Wachtel, and Hechter[2]) have suggested that prostigmine methylsulfate might precipitate a blood flow in women whose periods were delayed by causes other than endocrine dysfunction or early pregnancy. These workers[2] have further attempted to demonstrate that this action is so specific that it could be used as a diagnostic measure in differentiating a "physiologic delay" from early pregnancy, "with the same degree of accuracy as is possible with the Aschheim-Zondek test." Weisman,[3] however, criticized the rationale of the procedure as a differential diagnosis since so many qualifying conditions (puberty, menopause, systemic disorders, endocrinopathies, etc.) were introduced. Winter,[4] furthermore, clinically demonstrated failures of this procedure in inducing menstruation when gravidity was not present. Greenhill[5] agrees essentially with these authorities.

Soskin and others suggest that prostigmine be administered in daily doses of from 1 to 2 c.c. (1:2,000) for three consecutive days. If bleeding is induced, the patient is considered to be nonpregnant. They state that clinical evidence is available to demonstrate that prostigmine is nonabortive, nonecbolic, will not induce premature labor, and has no effect on the uterine musculature even at full term (Schofer[6] and Spoto[7]).

Since the original publication,[2] much clinical material has become available for study of the menstrual phenomena induced with prostigmine. It is the purpose of this investigation first to assay the efficacy of this drug as a diagnostic measure for determining early pregnancy; and second, to disclose as far as possible the actual modus operandi of the drug in producing menstrual bleeding.

GENERAL METHODS

A complete history, including a menstrual history, was taken on all patients. Physical examination, with special attention being given to a complete pelvic examination, was done routinely. Furthermore, all

stigmas of endocrine origin were carefully noted. In all cases where examination left doubt as to gravidity, the Friedman modification of the Aschheim-Zondek test was done routinely.

In order to determine the efficacy of this drug as a diagnostic test for pregnancy, only those patients who asked for such a diagnosis are included in Tables I to IV. In all, 90 such patients, complaining of temporary amenorrhea, were treated with injections of prostigmine methylsulfate. All injections were given intramuscularly, one injection per day, for periods ranging up to three days. Depending on the weight of the patient and the duration of the amenorrhea, the amount of prostigmine used was either 1 or 2 c.c. (1:2000) per injection. If the menstrual flow was precipitated before the series was completed, further injections were discontinued.

Excluding temporary vertigo and nausea which were present in about 40 per cent of all cases, no untoward effects were noted, except in one case, where after the third injection the patient collapsed. Shock lasted for about fifteen minutes, during which time there was loss of sphincter control, slowing of respiration, and almost complete disappearance of the pulse. Treatment was started and recovery was spontaneous and complete. No explanation for this peculiar reaction can be offered.

EXPERIMENTAL RESULTS

Originally this work was undertaken to verify the value of prostigmine as a test for possible pregnancy, based on the fact that if the patient did not bleed after a series of three injections, she was to be considered gravid. Patients are divided into three groups, according to results obtained, as correlated with either the physical findings or the Aschheim-Zondek tests:

1. Those patients diagnosed as not pregnant who bled after the injection of prostigmine.
2. Those patients who either were diagnosed as pregnant, or who subsequently proved to be pregnant who did not bleed as the result of the action of prostigmine.
3. All other patients, in whom results with prostigmine failed to agree with other observations.

As has been mentioned previously, the following series is limited to only those cases where a suspicion of pregnancy on the part of the patient existed. No attempt to induce menstruation was made where the amenorrhea was due to glandular involvement or where no indication for the precipitation of the flow existed. Table I represents in brief, the histories of 57 cases, proved nonpregnant either by physical examination, by the Aschheim-Zondek test, or by further observation in which the action of prostigmine was sufficient to bring about the delayed vaginal bleeding.

In reviewing Table I, one to three injections (average 2.4) of from 1 to 2 c.c. of a 1:2000 solution of prostigmine methylsulfate were given to 57 women whose ages varied from 18 to 44 years, resulting in starting delayed menstrual flow. Bleeding occurred in from one to seventy-two hours after the last injection had been administered, and the average lapse of time was fourteen hours. This interval was not related in any

TABLE I. SUCCESS OF PROSTIGMINE IN INDUCTION OF DELAYED MENSTRUATION (NONPREGNANT)

GROUP	NO. CASES	DELAY*	AVERAGE DELAY	AVERAGE NUMBER OF INJECTIONS†	RESPONSE
I	5	3-7 da.	5.5 da.	2-3	1 to 24 hours (average 12.5 hours) after last injection
II	25	8-14 da.	11.4 da.	2-3	3 to 36 hours (average 11.4 hours) after last injection
III	22	2-4 wk.	24 da.	2-4	1 to 72 hours (average 11.1 hours) after last injection
IV	5	Over 4 wk.	6.2 wk.	2-3	1 to 24 hours (average 15.5 hours) after last injection
Total	57	3 da.-8 wk.	17.7 da.	2-4	1 to 72 hours (average 14 hours)

*Absence of pregnancy determined by: Aschheim-Zondek test, 28; physical examination and follow-up, 29.
†Injections: 1 c.c. of 1:2000 solution of prostigmine methylsulfate.

way either to the amount, or the number of injections, nor was it associated with the duration of amenorrhea preceding injection therapy. This delay varied in this series from three days to two months, the average being 17.7 days. All patients were diagnosed as nonpregnant either by physical examination or by the Aschheim-Zondek test.

Obversely, in contrast with the resultant bleeding following prostigmine in the nonpregnant, was the lack of flow in cases in which a definite gravidity was present. Diagnosis of pregnancy was made as often as possible by physical examination, and was checked in most instances by the Friedman test. Follow-ups to corroborate the diagnosis

TABLE II. FAILURE OF PROSTIGMINE IN INDUCTION OF DELAYED MENSTRUATION IN PREGNANCY

GROUP	NO. CASES	DELAY*	AVERAGE DELAY	AVERAGE NUMBER OF INJECTIONS†	REMARKS
I	4	4-7 da.	6 da.	3+	No bleeding
II	6	8-14 da.	11.8 da.	3+	No bleeding
III	8	14-28 da.	21.2 da.	3+	One patient spotted after third injection; no other bleeding
IV	3	6-12 wk.	8.6 wk.	3+	No bleeding
Total	21	4 da.-12 wk.	21.6 da.	3+	

*Pregnancy diagnosed by: Aschheim-Zondek test, 9; physical examination, 12.
†Injections: 1 c.c. of 1:2000 solution of prostigmine methylsulfate.

TABLE III. FAILURE OF PROSTIGMINE TO DIAGNOSE PREGNANCY

NO.	NAME	AGE	GRAVIDITY	CATAMENIA	DELAY	STATUS	INJECTION	RESULTS
43	E. S.	46	0	15/28/4; periods decreasing in amount during last year; few menopausal symptoms (subjective) present	30 days	Physical examination negative; Aschheim-Zondek negative	4 × 3	None
44	D. G.	48	iv	10/27-29/6; no subjective symptoms; interval increased by 2 weeks during last year	30 days	Slight enlargement of uterus; Aschheim-Zondek negative	4 × 2	None; spotted for 1 day about 2 months after injection
45	N. S.	42	ii	11/28/3-5; no irregularity of menses; some menopausal symptoms (?)	Approximately 1 month	Small soft uterus + Chadwick's sign; Aschheim-Zondek negative	3 × 2 1 × 3	No results in 1 week; no further follow-up
46	F. L.	20	0	17/25-27/3; periods irregular; married 3 months	Approximately 5 weeks	Soft uterus; not enlarged; Aschheim-Zondek negative	3 × 2	No result; bled spontaneously 3½ weeks after last injection
64	A. S.	26	0	16/6 weeks/3; no irregularity of periods; no endocrine stigmas	4 weeks	Physical negative; Aschheim-Zondek negative	3 × 1	No result in 10 days
49	D. J.	22	0	14/30-35/7	? 2 weeks	Patient felt pregnant; Aschheim-Zondek doubtfully positive	3 × 2	Stained after second injection; bled profusely after third, with cramps and clots
65	R. B.	26	0	15/26/3; no irregularities of periods	9 days	Pregnant to examination. No Aschheim-Zondek done	3 × 1	Bled; examined 1 month later and was 10 weeks gravid
82	F. T.	29	i	13/29-31/5; no irregularity of periods, 6 months post-partum	15 days	Not pregnant to examination, Aschheim-Zondek negative; very obese	3 × 2	No bleeding in 5 days
83	E. B.	44	iv	12/28/5; decreased flow for 6 months	Approximately 3 weeks	Not pregnant to examination; no atrophy of genitals	3 × 1	Bled 1 week after last injection (skipped one entire cycle)
47	E. M.	31	iii	14/25-31/5; severe dysmenorrhea	11 days	Pregnant to examination ? of cystic ovary on right	3 × 1	Bled for 2 days following last injection; bled 1 month later for 3 days; diagnosed as continued pregnancy
69	S. C.	26	ii	12½/21-28/5; dysmenorrhea; oligomenorrhea	18 days	Uterus small; tender in right adnexa; Aschheim-Zondek positive	2 × 1	Spotted 17 hours after second injection; ? of ectopic. Operated for "emergency" 5 days later
67	W. M.	29	0	12/28/3; mild dysmenorrhea	14 days	Aschheim-Zondek negative	2 × 1 1 × 2	No bleeding after third injection. Bled spontaneously and normally 56 days after the last menses

and also to determine the effect of the prostigmine on the gravidity were made frequently. Twenty-one patients who were pregnant and who were injected with prostigmine without resultant bleeding are presented in Table II.

These 21 patients (Table II) ranged in age from 17 to 40 years, averaging 26.2 years, and had experienced zero to four previous pregnancies (average 1.2). The minimal number of injections given any patient was 3, and the dosage varied from 1 to 3 c.c. of the solution. The pregnancy, as calculated from the menstrual delay, was present from four days to six weeks, with an average of 21.6 days. No bleeding resulted from these injections with the exception of slight spotting after the third injection in Case 50. It is further of interest to note that prostigmine gave a correct response in one instance before the Aschheim-Zondek test became positive (Case 103).

As has been stated, a total of 90 patients, all suspicious of being pregnant, were injected with prostigmine in an attempt to make a definite diagnosis. Of these, 78 reacted in accordance with their physical status. In contradistinction to the results presented above, are the following 12 patients (Table III) in whom incorrect menstrual reactions to the drug occurred.

Before discussing the effects noted with prostigmine, it would be desirable to summarize briefly, in table form, the results obtained in the above series. In review, therefore, 90 cases of delayed menstruation, treated as described, gave results as shown in Table IV.

TABLE IV. PERCENTAGE OF ERROR OF PROSTIGMINE AS A "DIAGNOSTIC PREGNANCY TEST"

Total number of cases injected		90	
Patients diagnosed nonpregnant who bled	57		
Patients diagnosed as pregnant who did not bleed	21		
Total correct results	78		
Percentage correct results			86.6%
Patients not pregnant who did not bleed	8		
Patients pregnant who bled (including possible ectopic)	4		
Total errors	12		
Percentage error			13.4%

DISCUSSION

Eighty-seven per cent of 90 consecutive nonselected cases of delayed menstruation where early pregnancy was suspected gave correct results when tested with intramuscular injections of prostigmine methylsulfate. However, if this drug is to be considered as a substitute for the standard, harmless, and technically simple Aschheim-Zondek test, it should be

more accurate in all cases, regardless of the age, physical development or endocrine status of the patient, or of the presence of pelvic or systemic pathology.

It is of interest, therefore, to study in greater detail, those cases where prostigmine gave an incorrect diagnosis. This occurred in 12, or in 13 per cent, of the total number of patients tested. In 3 of these, no definite pathology could be determined which would explain the inability of prostigmine to produce bleeding, regardless of the fact that no pregnancy was present (Cases 46, 64, and 82). Four cases (Cases 43, 44, 45, and 83) may be classified as beginning climacteric, since some few menopausal symptoms were present. Five cases (Cases 49, 47, 69, 65, and 67) are of sufficient interest to report in more detail. Brief résumés of these case histories are as follows:

CASE 49.—Mrs. D. J., aged 22 years, who had been married one year, was first seen on Jan. 16, 1941, complaining of a menstrual delay of approximately two weeks, frequency of urination, and engorgement of the breasts. Past history was negative. Menstrual history 14/30-35/7; moderate flow, no clots, no dysmenorrhea. There had been no previous pregnancies. Her last menstrual period occurred on Dec. 2, 1940 (?). Physical examination essentially was negative. Pelvic examination revealed a slightly enlarged, softened uterus in first-degree retroversion. Hegar's sign was positive. Breasts were enlarged and heavy. Areolae were darkened slightly. The Aschheim-Zondek test on Jan. 17, 1941, showed enlarged follicles, but no hemorrhage or hemorrhagic follicles. Test was reported as "doubtful" on Jan. 19, 1941; however, it was felt that the patient was pregnant.

On January 16, 17, and 18 she received 2 c.c. of 1:2000 solution of prostigmine methylsulfate. No bleeding occurred after the first injection. There was some spotting after the second, and profuse bleeding, with clots and cramps following the third. This lasted for four days, after which there was a normal flow for three additional days.

The next menstrual period occurred on Feb. 16, 1941, and was normal.

CASE 65.—Mrs. R. B., aged 26 years, complained of menstrual delay of nine days. Catamenia 15/26-8/3; no dysmenorrhea, moderate flow. Physical examination essentially was negative. Breasts were heavy and sensitive. Pelvic examination: external genitals, normal; vagina, normal, except for positive Chadwick's sign. Cervix rather soft; uterus slightly enlarged. Diagnosis of early gravidity made. Aschheim-Zondek test not done.

On February 13, 14, and 16 she received 1 c.c. of 1:2000 solution of prostigmine. Bleeding started about five hours after the last injection was given. Patient bled similarly to a normal period for four days.

On Mar. 24, 1941, she returned to the clinic, again complaining of a delay of eight days. Prostigmine was again administered, despite the fact that a definite nine to ten weeks' gravidity was found. On March 24, 25, and 26 she received 1 c.c. of 1:2000 prostigmine without subsequent bleeding.

CASE 47.—Mrs. E. M., aged 31 years, was first seen on June 15, 1941, with a complaint of menstrual delay of eleven days. There were no

subjective signs of pregnancy. Past history essentially was negative. Pelvic examination gave the impression that the uterus was slightly enlarged, and an ovarian cyst could be felt on the right ovary. Last menstrual period occurred on May 6, 1941.

On June 15, 16, and 17 she received injections of prostigmine. Following the third injection she bled for two days. On July 20 she again bled for three days and a diagnosis of a three months' pregnancy was made at that time. Diagnosis was confirmed by follow-up examinations. Patient carried through the seventh month and delivered a premature infant.

CASE 69.—Mrs. S. C., aged 26 years, gravida ii. Catamenia 12½/21-28/5. Past history negative. Menstrual history unimportant except for mild dysmenorrhea and slight oligomenorrhea. Last menstrual period occurred on August 12. She was seen on September 16 complaining of a delay of eighteen days. Physical examination was negative. Pelvic examination: uterus was small but slightly softened. There was some tenderness, but not marked, in the right adnexa. Aschheim-Zondek test was positive (September 20). On September 15 and 16 she received injections of 1 c.c. of prostigmine. She spotted approximately seventeen hours after the last injection, and the tenderness on the right side seemed to be increased. Injections were discontinued for fear of ectopic gestation. Although the patient was told to report back to the clinic she did not, but indirectly it was heard that five days later she was operated upon for some emergency abdominal condition.

These four cases, therefore, must be classified as false negatives since all were gravid, yet bled after prostigmine had been administered. In Case 49, although the result of the Aschheim-Zondek test was not conclusive, both the subjective symptoms and the increased size of the uterus on bimanual examination left the distinct impression that pregnancy existed. The possibility of gravidity, therefore, must be admitted, together with the possibility of spontaneous abortion, or induced abortion as the result of the injections of prostigmine. However, none of the above assumptions can be definitely proved. In the second case (Case 65), although no Aschheim-Zondek test was performed, there was the definite impression that the patient was gravid. Although this patient bled similar to a normal menstruation, examination one month later definitely proved the original diagnosis, since the size of the uterus had increased to that of a nine or ten weeks' gravidity. In order to verify this, prostigmine was again administered, but without any resulting bleeding. Similarly in Case 47, bleeding followed injections despite the fact that the patient was pregnant. In Case 69, although proof is not definitely obtainable, it is assumed from the history, physical examination, and follow-up, that the patient had an ectopic pregnancy, despite which she bled after two injections.

SUMMARY

Prostigmine methylsulfate successfully differentiated early pregnancy from temporary amenorrhea by inducing delayed menstrual flow in about 87 per cent of 90 cases that were thus tested. Patients were not selected and no distinction as to menopausal state, endocrine status, pelvic pathology, etc., was made. Injections were given only to those patients who definitely requested an opinion as to whether or not they

were pregnant. The responses to prostigmine were checked against the findings at physical examination and, where necessary, against the Aschheim-Zondek test. Follow-up examinations to verify diagnoses were made as often as possible.

The response to the drug is fairly rapid. In the nongravid, bleeding started after an average interval of fourteen hours following the last injection. The average number of injections was 2.4. If no response was elicited after a maximum number of three injections the patient was considered to be pregnant. Translating these statistics into elapsed time, the average interval for diagnosis of pregnancy with prostigmine is at least seventy-two hours, compared with a maximum of forty-eight hours with the Aschheim-Zondek technique. Should the time element ever be an important factor for the establishment of a diagnosis, the Aschheim-Zondek test is therefore superior. However, the latter is known to err, especially on the negative side, in the early stages after the first skipped period. This is to be contrasted with the fact that all 6 patients tested during the first week of amenorrhea were accurately diagnosed as pregnant by prostigmine. This is further demonstrated by Case 103, where prostigmine produced a correct diagnosis as early as one week after the skipped period, even though at this time the Aschheim-Zondek test had not yet become positive.

Discrepancies of diagnosis were noted both in positive and negative responses. Eight patients who were not gravid continued their amenorrhea, despite the injections; 4 patients who were pregnant bled following the injections. Herein lies the greatest hazard in the use of this drug. The possibility of inducing abortion, slight as it may be, would completely obviate this test in all cases where pregnancy is extremely desired, where relative sterility is involved, and where there has been a previous history of repeated spontaneous abortions.

Moreover, other factors than those of the actual statistical studies are present, and must be analyzed and considered before the test can be evaluated. The obstetrician divides all patients into two classes: those who will not tolerate pregnancy, and those who are anxious and desirous for offspring. These latter, when delayed, even though they are not pregnant, might easily misinterpret the bleeding following the injections of prostigmine, and suspect that they have been aborted. This is especially true in pseudocyesis. Furthermore, in any case where unwanted bleeding occurs, the attending physician is placed on the defensive, and despite explanations, will almost surely lose the confidence of his patient.

On the other hand, prostigmine, as a test for pregnancy, possesses a definite psychologic advantage, from the patient's viewpoint, that the doctor "is doing something positive" both in the way of diagnosis and of therapy if the delay is physiologic. Although the physician realizes that it is not essential to bleed at clocklike intervals, it is often difficult to convince a worried female who knows only that suspended menses is indicative of pregnancy. There is no question, therefore, that the use of

this drug, with its diagnosis dependent upon the resumption of menstrual function, will keep a great many women from unnecessary manipulations at the hand of the abortionist. Furthermore, the resumption of the normal menstrual rhythm in the nonpregnant is a great psychologic factor, especially when pregnancy is not desired at the time that the menses is delayed.

The use of prostigmine methylsulfate as a therapeutic measure for the regulation of the menstrual rhythm has not as yet been fully examined and studied. However, its field of usefulness would seem to be here, rather than in the field of diagnosis. Further experimentation is now in progress to determine the exact nature and physiology of this drug on the female generative tract.

CONCLUSIONS

Prostigmine methylsulfate was successfully used in the differentiation of amenorrhea due to pregnancy from amenorrhea due to other causes in 86.6 per cent of 90 cases. Diagnostic errors occurred in both pregnant and nonpregnant cases. Four patients who were pregnant bled; 10 continued their amenorrhea despite nongravidity. Although statistical results are favorable, because of the possible abortion factor, prostigmine should not be used where pregnancy is urgently desired, where relative sterility existed, where a history of repeated abortions is elicited, or when pseudocyesis is present. These contraindications, together with those mentioned in previous publications, namely, endocrine dysfunction, local pelvic changes, possible ectopic pregnancy, menopause, etc., make the drug, as a diagnostic procedure, of extremely small value. Prostigmine, however, is of real worth as a therapeutic measure in temporary amenorrhea after the diagnosis of nongravidity has already been established.

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CONSERVATIVE TREATMENT OF PELVIC INFLAMMATION WITH THE NEWMAN THERMO-FLO

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THE incidence of pelvic inflammatory disease in a gynecologic clinic is high. It is also an important factor, contributing to chronic ill health so frequently seen in this group of women, and it often forms a basis for such common complaints as abdominal pain, backache, dysmenorrhea, menstrual irregularity, vaginal discharge and the neurasthenic syndrome. Whatever plan of treatment is employed, the conservative management of pelvic inflammation merits most careful consideration, first, because of good results that have been reported by the use of various conservative measures, and second, because of the danger and unsatisfactory results that frequently follow more radical operative intervention.

Heat applied to the pelvis as a therapeutic measure has been used in various forms since the time of Hippocrates who described the simple hot vaginal douche. Other methods subsequently introduced include, heated lead shot poured into the vagina as described by Holden and Gurnee,[1] the hot intravaginal douche which was condemned by Emmet,[2] the prolonged vaginal douche as described by Gellhorn,[3] the Elliott apparatus, diathermy, and short wave therapy.

Newman,[4] in 1939, described the thermo-flo, which marks a definite advance in the application of intravaginal heat. This apparatus was used in our work in the treatment of pelvic inflammatory conditions at the Cook County Hospital and the Research and Educational Hospital, Chicago. It was proved to be an effective, yet simple and safe, device, and free from the objections which have been raised against the other methods.

Falls, Newman, and Kobak[5] published a preliminary report on the use of this apparatus on gynecologic patients at Research and Educational Hospital and Cook County Hospital, which was read in September, 1939, at the American Congress of Physical Therapy, in New York City. In general, the results in this series of 71 cases correspond with those obtained in the series here reported.

Greenhill[6] states that he has used the Newman thermo-flo successfully in the treatment of pelvic inflammatory disease.

DESCRIPTION OF APPARATUS

The Newman thermo-flo apparatus (Fig. 1) as a simple device for the application of intravaginal heat, utilizes circulating air as the heating medium and in this respect differs fundamentally from other methods. Essentially, the apparatus is composed of a motor-driven fan which circulates heated air that is applied to the pelvis by means of a bicornuate-

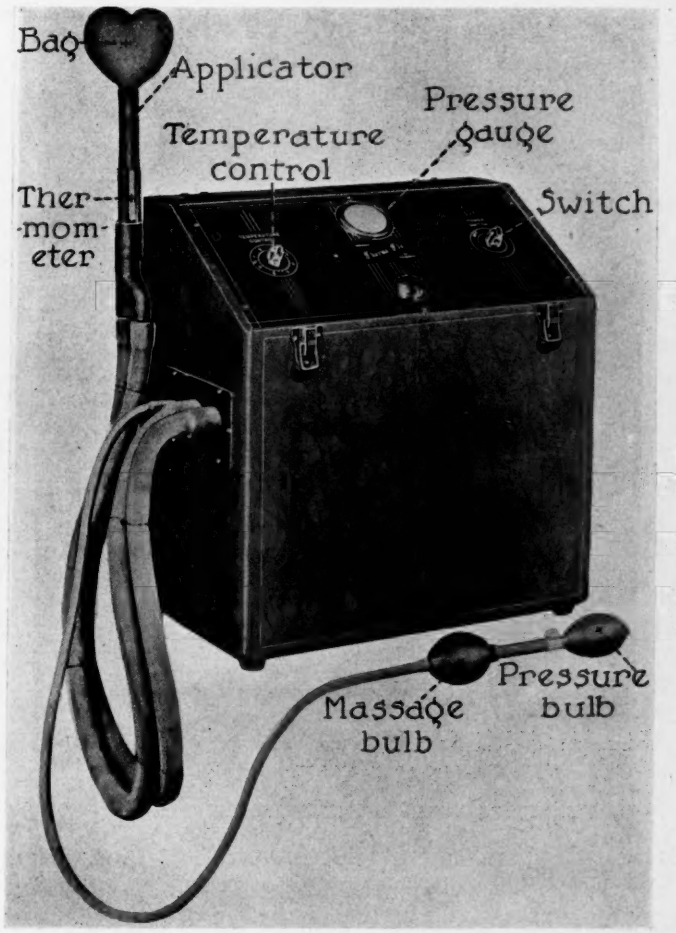

Fig. 1.—Newman thermo-flo.

shaped, inflated, thin rubber applicator bag. Temperatures up to 132° F. are automatically maintained by thermostatic control and registered by a thermometer extending into the applicator bag. The air pressure within the distended bag is regulated by means of a rubber bulb and is indicated on the pressure gauge. Uniform distribution of heat over a large surface of the vagina, negligible weight of an air-filled bag, relative

freedom from potential burns and complete comfort during treatment are a few of the important advantages of the Newman thermo-flo apparatus.

Adair,[7] reporting the work done with this apparatus at the Chicago Lying-in Hospital, states that among the advantages of the thermo-flo may be mentioned the extremely simple mechanism, the ease and rapidity of its operation, and most important, the greater comfort afforded the patient.

Counseller[8] objects to the use of a nondistensible electrode in the vagina because the rugae or folds prevent even distribution of heat and render the vaginal mucosa more susceptible to burns.

Fig. 2.—Roentgenograph of pelvis showing inflated rubber bag in the vagina.

Fig. 2 shows roentgenologically the position of the inflated bag in the vagina.

PHYSIOLOGIC EFFECTS OF LOCAL HEAT

When heat is applied locally to the body, the increased blood and lymph circulation due to dilatation of the arteries, arterioles, and capillary bed, is chiefly responsible for the desired therapeutic effect. If the process is kept within physiologic limits, tissue injury will not result. Increased circulation through the tissues promotes tissue metabolism, augments oxygenation of the cells, and hastens the exchange of the metabolites.

Bier[9] called attention to the value of producing active hyperemia by means of heat for the destruction of an infective process.

Michel and Taube,[10] in reporting upwards of 1,000 cases treated with pelvic heat, are of the opinion that any heat capable of being applied

without damage to the tissues kills only the organisms which come in direct contact with the applicator, and that the organisms deep in the tissues are only attenuated, so that their destruction is more easily accomplished by the normal defense mechanism.

Locally, there is noted a marked increase in phagocytic leucocytes and more rapid absorption of inflammatory exudates. A general leucocytosis is also produced after treatment in most cases, an average increase of 18 per cent.

CLINICAL RESULTS

We have observed in our series, 200 cases of pelvic inflammatory disease, which were classified as accurately as possible, into three major groups. This classification is based upon the information obtained from the history, physical findings, and bacteriologic studies in the individual cases.

I. Gonococcal infections. This included:
   - A. Chronic bilateral salpingo-oophoritis.
   - B. Chronic bilateral salpingo-oophoritis with unilateral or bilateral tuboovarian masses.
   - C. Chronic diffuse pelvic inflammatory disease, the so-called "frozen pelvis."

   Most of the patients in this gonococcal series present a history of one or more exacerbations of their pelvic infection over a varying period of time.

II. Nonspecific pelvic infections.
   This included primarily the puerperal and septic-abortion cases, caused mainly by the streptococcus.
   - A. Chronic pelvic cellulitis, parametritis and tubo-oophoritis.

III. Postoperative residual pelvic inflammatory disease. This included both the gonococcal and nonspecific groups.

We have classified the clinical results of treatment into four groups, namely: Complete cure, marked improvement, moderate improvement and slight or no improvement (Fig. 3).

The criteria used for classification included an accurate appraisal of symptomatic improvement stated by the patients and frequent check-up examinations of the pelvis, in most instances by the same clinician. The latter anatomic findings were mainly stressed in this analysis. The factors used in making this clinical classification, to indicate improvement, included lessened or absent tenderness, diminution in size of inflammatory masses, resolution of broad ligament thickening and induration, and increased mobility of the pelvic structures.

Cases designated as completely cured include those with absolute symptomatic relief and apparently complete regression of tangible pathologic findings.

Cases designated as markedly improved include patients with absolute symptomatic relief in most cases, and marked, though not complete, regression of tangible pathologic findings.

Cases designated as moderately improved include those with satisfactory symptomatic relief even in the presence of definite pathologic changes.

Cases designated as slightly or not improved include those with some symptomatic relief but little or no alteration in the pathology present.

Gonococcal Infections.—This major classification was further subdivided according to the degree and extent of pathologic involvement of the pelvic structures. This varied from mild bilateral salpingo-oophoritis

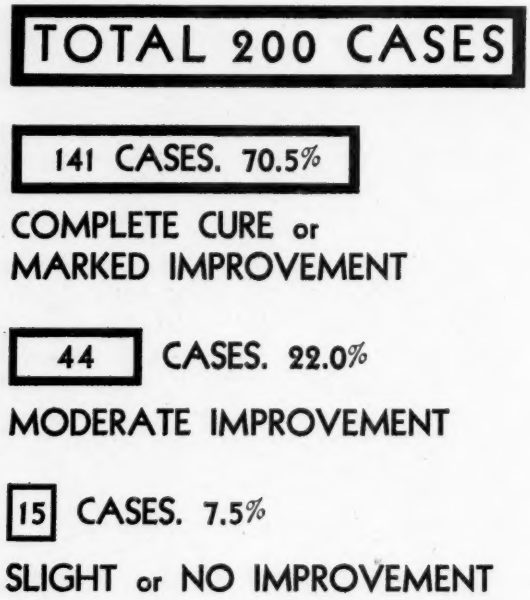

Fig. 3.—Results of 200 cases of pelvic inflammatory disease treated with the thermo-flo.

with pelvic peritonitis, to those of more severe nature with purulent salpingitis and tuboovarian abscess, and finally to the extensive and diffuse, exudative, pan-pelvic peritonitis known as the "frozen pelvis."

Our first series included 87 cases of bilateral salpingo-oophoritis (Table I); of these 75 were chronic: 12 were subacute. Chronicity was designated, if the symptoms and findings persisted for three months or longer. In these groups, 51 patients were white, 36 colored. The duration of symptoms varied from three months to thirteen years, and the age incidence averaged twenty-five years. The number of thermo-flo treatments per patient varied from 6 to 32, with an average of 14. Eight cases were classified as completely cured; 54 as markedly improved; 18 as moderately improved and 7 as slightly or not improved. It is interesting to note that 5 of the 8 patients classified as completely cured, subse-

TABLE I. BILATERAL SALPINGO-OOPHORITIS; 87 CASES

	NO. OF CASES	AGE	DURATION OF SYMPTOMS	NO. OF TREATMENTS	COMPLETE CURE	MARKED IMPROVEMENT	MODERATE IMPROVEMENT	SLIGHT OR NO IMPROVEMENT
Subacute	12	17 to 56 yr. Av. 25	2½ mo. to 13 yr.	6 to 32 Av. 14	2	7	2	1
Chronic	75				6	47	16	6
Total	87				8	54	18	7

quently became pregnant after sterile periods of two to four years. One patient who was subsequently operated upon because of complaints referable to a retroversion was found to have patent tubes on retrograde insufflation. It was observed during the course of treatment for the upper pelvic tract infections that many cervical erosions became healed. The complication of gonococcal arthritis was noted once in this series, during the course of a subacute exacerbation of the pelvic infection, in a negress.

Our second series included 33 cases of bilateral salpingo-oophoritis with unilateral or bilateral tuboovarian masses (Table II). Of these 29

TABLE II. BILATERAL SALPINGO-OOPHORITIS WITH UNILATERAL OR BILATERAL TUBO-OVARIAN MASSES, 33 CASES

	NO. OF CASES	AGE	DURATION OF SYMPTOMS	NO. OF TREATMENTS	COMPLETE CURE	MARKED IMPROVEMENT	MODERATE IMPROVEMENT	SLIGHT OR NO IMPROVEMENT
Subacute	4	17 to 52 yr. Av. 26	2 mo. to 10 yr.	6 to 26 Av. 16	0	2	1	1
Chronic	29				0	22	5	2
Total	33				0	24	6	3

were chronic; 4 subacute. The duration of symptoms varied from two months to ten years; the age incidence averaged 26 years. The number of thermo-flo treatments per case varied from 6 to 26, average 16. The group includes 21 white, and 12 colored patients. It will be noted that there were no cases classified as complete cure in this group based on pathologic findings. The majority (24), however, were classified as markedly improved; 6 as moderately improved and 3 cases as slightly or not improved. Two patients with tuboovarian abscesses were drained per vaginam and then given thermo-flo treatments. Six patients were operated upon because of inadequate response to therapy and for economic reasons. One of these cases with moderately advanced adnexal pathology and retroversion received a course of 8 preoperative treatments and at operation the adnexa appeared sufficiently normal to warrant their retention. A uterine suspension operation was performed.

Our third series included 12 cases of chronic pelvic inflammatory disease, "frozen pelvis" (Table III). In this group the duration of symptoms varied from three months to eight years; the age incidence varied from twenty to forty-two years, an average of 30 years. The number of thermo-flo treatments varied from 9 to 18, with an average

TABLE III. CHRONIC PELVIC INFLAMMATORY DISEASE (FROZEN PELVIS), 12 CASES

NO. OF CASES	AGE	DURATION OF SYMPTOMS	NO. OF TREATMENTS	COMPLETE CURE	MARKED IMPROVEMENT	MODERATE IMPROVEMENT	SLIGHT OR NO IMPROVEMENT
12	20 to 42 yr. Av. 30	3 mo. to 8 yr.	9 to 18 Av. 14	0	8	4	0

of 14. Seven patients were white and 5 colored. In one instance a pelvic abscess was drained through a posterior colpotomy incision. One patient was subsequently operated upon because of associated fibromyomas and protracted menorrhagia. Eight cases were classified as markedly improved and 4 as moderately improved.

Nonspecific Pelvic Infections.—This classification comprised postabortal, postpartum, and postoperative (Cesarean section) cases, primarily streptococcal in origin (Table IV), a total of 35 cases.

TABLE IV. PARAMETRITIS (POSTABORTAL, POSTPARTUM, POSTOPERATIVE), 35 CASES

	NO. OF CASES			AGE	DURATION OF SYMPTOMS	NO. OF TREATMENTS	COMPLETE CURE	MARKED IMPROVEMENT	MODERATE IMPROVEMENT	SLIGHT OR NO IMPROVEMENT
	POSTABORTAL	POSTPARTUM	POSTOPERATIVE							
Acute	8	1	1	17 to 40	1 wk. to	7 to 27	0	7	3	0
Subacute	7	0	2	yr.	5 yr.	Av. 14	1	6	2	0
Chronic	7	8	1	Av. 27			1	8	3	4
Total	22	9	4				2	21	8	4

This series included 24 cases of septic abortion, 8 of which were acute, 7 subacute and 7 chronic; 9 cases followed full-term delivery and 4 cesarean sections. The duration of symptoms varied from one week to five years; the age incidence from 17 to 40, an average of 26.5 years. The number of thermo-flo treatments varied from 7 to 27, averaging 14. Twenty-two patients were white and 13 colored. Of this group, 2 became pregnant following treatments. In two instances a pelvic abscess was drained per vaginam. One postoperative case, following a total hysterectomy for fibroids and chronic cervical pathology, developed a fulminating, rapidly spreading cellulitis which responded favorably to heat treatments. Two cases were classified as completely cured; 21 as markedly improved; 8 as moderately improved and 4 as slightly or not improved. Generally speaking, regression of the pathologic changes in this group appeared to be more complete in the severe cases than was noted in those of gonococcal origin.

Postoperative Residual Pelvic Inflammatory Disease.—This classification included both the gonococcal and nonspecific groups, in which operation was previously performed on one or more occasions for such infections (Table V).

This series of postoperative residual pelvic inflammatory disease consisted of 33 cases; 29 of which were chronic and 4 subacute. The duration of symptoms varied from four months to eight years; the age incidence was from twenty-four to forty-six, an average of 32.5 years. The number of thermo-flo treatments varied from 9 to 55, averaging 17.

Sixteen of the patients were white and 17 colored. One case was classified as completely cured, 23 as markedly improved, 8 as moderately improved, and 1 as slightly or not improved.

One patient was subsequently re-operated upon for an old broad ligament hematoma. Another received a series of 12 thermo-flo treatments and at subsequent operation an infected ovarian cyst was removed.

TABLE V. POSTOPERATIVE RESIDUAL PELVIC INFLAMMATORY DISEASE, 33 CASES

	NO. OF CASES	AGE	DURATION OF SYMPTOMS	NO. OF TREATMENTS	COMPLETE CURE	MARKED IMPROVEMENT	MODERATE IMPROVEMENT	SLIGHT OR NO IMPROVEMENT
Subacute	4	24 to 47 yr. Av. 33	4 mo. to 8 yr.	9 to 55 Av. 17	0	4	0	0
Chronic	29				1	19	8	1
Total	33				1	23	8	1

DISCUSSION

Although difficult to prove statistically, gonorrheal infection in the female pelvis is the most common cause of serious pathology, and is frequently productive of marked physical disability and sterility in the female. In recent years many authors have stressed the advantages of conservative management of pelvic inflammatory disease. From our experience we feel that the use of this form of intravaginal heat should definitely be added as an important factor in such management. We also feel that this form of treatment is a definite adjuvant pre- and postoperatively, particularly for the more extensively involved cases. Certainly, in those cases which subsequently come to operation, the quiescent phase of pelvic infection produced by this method of heat application produces definite decrease in morbidity and mortality.

Many of the patients seen at large charitable institutions, such as the ones from which this study was obtained, must, of economic necessity, be quickly restored to good physical health. Hence, surgical intervention is practiced much more freely than in other economically more independent strata of society. These factors played an important role in determining operative intervention in many of the 17 surgical cases in our series.

It is of great importance that chronic foci of infection in the lower genital tract be adequately treated in conjunction with the conservative treatment of the upper pelvic infection, to minimize the danger of autoreinfection. Unless there exist pressing indications for immediate operation in pelvic inflammatory disease, we suggest a trial period of conservative treatment for three months; twice or three times weekly, in practically all cases, before surgery is contemplated.

Some months ago, we decided to try intravaginal heat therapy in the treatment of puerperal infection, including postabortal, post-partum and postoperative cases. Although our series is not large enough at this

time to draw conclusions, we feel that thermo-flo treatment can be advocated as a safe procedure and a real adjuvant in the therapy of such conditions. The results of a much larger group of similar cases as yet unpublished, tend to fully support these views. The pelvic heat therapy, together with the sulfonamide drugs, has made the clinician somewhat less fearful in the management of these severe streptococcal infections of the pregnant uterus.

The clinical course of these cases as contrasted to the gonococcal group, appears to be much more rapid in most instances, with a more complete resolution of pelvic pathology. In this group, particularly the acute and subacute cases, treatment once or twice daily for one hour is advocated, especially during the patient's hospital stay. At present, we are cautiously extending the indication for heat treatment to include a study of prolonged intravaginal heat application, from eight to twelve hours, particularly in the more severe septic cases.

The series designated as postoperative residual pelvic inflammation contained many cases in which conservative surgery had been practiced, with resultant residual pathology. Exacerbations or external reinfections were frequently responsible for the recurrent clinical manifestations. Many patients possess the inherent tendency to develop abundant adhesions. We feel that the intravaginal heat may have aided these patients by stimulating pelvic circulation and causing a resorption of the residue.

It was noted in the course of treatment of many of these cases that concomitant bladder and rectal infections were clinically improved. The location of these organs makes possible their inclusion in the exposure to heat in the distended vagina.

In many instances of sterility, when tubo-oophoritis is a predominant causative factor, we feel that a trial of intravaginal heat therapy is warranted. In our series, 7 patients with previous histories of sterile periods of from two to four years, became pregnant after a series of thermo-flo treatments. Although this is not a large group, we feel justified in advocating this conservative measure, since surgical tubal reconstruction is rarely successful.

Intravaginal pelvic heat therapy is not advocated as a panacea for the cure of all types of pelvic infections. We present it as a definite improvement in the manner of heat application in the conservative management of many of these cases. It must be realized, because of the varied pathology in many cases, as well as associated complicating pathology, that operative intervention will be the treatment of choice in some instances.

SUMMARY

1. The Newman thermo-flo apparatus, in our hands, has proved an effective method for the application of prolonged intravaginal heat. The

method utilizes heated air and presents advantages over other devices, because of simplicity of operation, comfort, freedom from potential burns, and because it gives uniformly effective application of pelvic heat.

2. Two hundred patients with pelvic inflammatory disease were treated with the thermo-flo, of whom 141 (70.5 per cent) showed complete cure or marked improvement; 44 (22 per cent) moderate improvement, while 15 (7.5 per cent) obtained slight or no improvement. (a) Gonococcal infections in 132 cases showed in 94 (71.2 per cent) complete cure or marked improvement; in 28 (21.2 per cent) moderate improvement; and in 10 (7.6 per cent) slight or no improvement. (b) Nonspecific pelvic infection observed in 35 cases produced in 23 (65.7 per cent) complete cure or marked improvement; 8 (22.9 per cent) moderate improvement, and 4 (11.4 per cent) slight or no improvement. (c) Postoperative residual pelvic inflammatory disease seen in 33 cases yielded 24 (72.7 per cent) completely cured or markedly improved; 8 (24.2 per cent) moderately improved; and 1 case (3.1 per cent) slightly or not improved.

3. Seven patients of the entire series presented additional complaints of sterile periods of two to four years and subsequently conceived after thermo-flo treatments.

4. Bladder and rectal inflammation associated with pelvic infection is favorably influenced by the use of intravaginal heat.

5. In cases of gonococcal, nonspecific, and postoperative residual infections of the pelvis, our clinical impression was that a more rapid and complete resolution of pathology and improvement of clinical symptoms takes place, in a shorter period of time, than with previous methods of treatment.

6. We recommend the use of intravaginal heat therapy (thermo-flo) as a pre- and postoperative measure, in suitable cases.

7. We wish to emphasize that the treatment of pelvic inflammatory disease by intravaginal heat (thermo-flo) does not replace operative therapy in all instances, particularly when associated pelvic pathology exists. In a large group of society, surgery is more frequently indicated because of economic dependency.

We are greatly indebted to Esther Stumbo, R.N., Chief Physical Therapist, Cook County Hospital, Chicago, for her aid in this work.

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VAGINAL IONTOPHORESIS OF A CHOLINE COMPOUND*

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A STUDY of vaginal iontophoresis of a choline compound was begun in 1933 to determine whether any beneficial effects could be produced by its use in cases of pelvic inflammation. Two previous communications by one of us have appeared in the literature,[1, 2] detailing the results obtained in a limited number of patients. Since then, reports by others,[3, 4] to whom we demonstrated this modality, have already been or are about to be published, which substantiate our original conclusions. Since our last publication, we have amplified our observations on patients with pelvic inflammation and have also had occasion to add other groups in this survey: those in whom diagnostic clarification was necessary, patients with ovarian cysts, and a number complaining of dysmenorrhea.

The original technique has already been described in detail.[1, 2] The only recent change made is in the strength of the mecholyl solution employed. We are now using a 0.25 per cent solution of mecholyl instead of a 0.5 per cent solution, with equally satisfactory results. This can be readily understood, because the amount of mecholyl driven into the tissues is entirely dependent upon the strength of the current and the duration of its flow. In the technique now used which permits 15 milliamperes of current to flow for twenty minutes, only a portion of the material in the 0.25 per cent solution is utilized, so that even further dilutions might still produce satisfactory results. We have not yet encountered any instance of shock during treatment which has required interruption of the treatment and the administration of atropine to counteract the mecholyl effect. The results obtained in a group of patients with acute or chronic pelvic inflammatory disease are shown in Table I.

*Mecholyl, a product of Merck & Co., Rahway, N. J.

TABLE I. ACUTE AND CHRONIC PELVIC INFLAMMATORY DISEASE, NONOPERATED (74)

TYPE	NO.	FIRST WEEK		FIRST MONTH		LATE FOLLOW-UP 1-7 YEARS		
		RELIEF	SLIGHT OR NO RELIEF	IMPROVED	NO IMPROVEMENT	CURED	NO IMP.	NOT FOUND
Bilateral salpingo-oophoritis with parametritis	38	36	2	33	5	28	3	7
Bilateral salpingo-oophoritis with retroversion	4	2	2	4		3	1	
Unilateral salpingo-oophoritis	25	20	5	24	1	19	1	5
Parametritis	7	7		6	1	6	1	
Total	74	65	9	67	7	56	6	12
Per cent	100	87.8	12.2	90	10	75.6	8.1	16.3

In all of these patients the results were evaluated by the subjective symptoms and the changes found on physical examination after treatment. Except in patients suffering from acute pelvic inflammation and pyrexia, the treatment was administered as an ambulatory procedure.

In this group of 74 patients, a striking effect was the rapid lessening of the patient's complaints, and these changes were noticeable within the first week. A follow-up on this group, in some instances as long as seven years after treatment, showed that of the 62 patients contacted, 90.3 per cent remained cured. The cure in this group consisted of the complete disappearance of all inflammatory exudate, and in the majority, restitution of the affected organs to normal. In 18 of the 56 patients considered cured, a slight residual thickening remained.

In an additional group of 11 patients with inflammatory adnexal involvement, operation was performed after varying periods of preliminary treatment by iontophoresis. The details of this group are set forth in Table II. There was no apparent improvement in only one of these patients re-examined later.

The group in which treatment was instituted for the diagnostic clarification of the nature of palpable pelvic masses included 17 patients. Nine of these patients were operated upon subsequent to therapy. The other 8 did not require or refused operation, and the details are set forth in Table III, A and B. In these 8 patients re-examined after a course of therapy, the residual pathology was determined by physical examination and the extent of change in the pelvic masses noted. In the 9 patients who were subjected to operation, actual visual evidence was available. It was noticeable that when inflammatory pelvic disease complicated coexisting noninflammatory pathology, the operative procedures were rendered considerably less difficult and extensive by the prior reduction of the inflammatory process.

A group of 17 patients diagnosed as having various types of ovarian cystoma was subjected to treatment for variable periods as indicated in Table IV. The results obtained were not uniform. In some instances, the cystic areas in the ovaries apparently disappeared. In 4 patients, subsequently operated upon, the variable outcome following treatment was confirmed, as the enlargements of the ovary consisting

TABLE II. OPERATIVE CASES

CHRONIC PELVIC INFLAMMATION

NO.	DIAGNOSIS	PREOPERATIVE FINDINGS	IONTOPHORESIS	OPERATION	PATHOLOGY	LATE FOLLOW-UP
1	Left salpingo-oophoritis; fibroid uterus	Intramural fibroid; left fornix filled with doughy, cystic, tender mass	1 month	Left ovary resected; adhesions liberated	Intestinal adhesions to left broad ligament and ovary; gigantic corpora fibrosa left ovary	1934, no improvement
2	Left salpingo-oophoritis	Left fornix filled with large hard mass, possible dermoid	2 weeks	1936, left tube and ovary resected; right tube, fimbriated end, resected	Omentum adherent to left tube and ovary. Ovary 3 inches in diameter. Cystic. Fimbriated end right tube closed	1940, cured tube patent
3	Bilateral salpingo-oophoritis. Third-degree retroversion; fibroid uterus	Right fornix filled with large cystic mass; left ovary cystic; uterus retroverted; hard, knobby	1 month	1937, ovary suspended; fibroid enucleated	Uterus bound down in cul-de-sac; fibroid; right ovary normal. Left recent rupture Graafian follicle; tubes showed evidence salping.-nodosum	1941, improved
4	Left tuboovarian mass. Metastatic carcinoma left ovary with infection	Mass in left fornix 4 inches in diameter	3 months	4/28/38, bilateral salpingitis; left oophorocystectomy; resection sigmoid	Ovary, serous cysts; tube showed scarring; bowel adenocarcinoma	Infection cured
5	Bilateral salpingo-oophoritis	Soft, tender mass filling right fornix to pelvic wall. Left tube and ovary thick and tender	6 weeks	8/4/36, adhesion freed; uterus suspended. Appendectomy	Uterus retroverted and to left. Left tube and ovary normal; right tube normal. Adhesions between right ovary and right broad ligaments	Cured

6	Acute bilateral salpingitis. Pelvic abscess; urethritis	10/16/34, right tuboovarian mass 3 inches in diameter. Left tube thick	3 months	Colpotomy, 9/12/34	Pelvis clear. Bartholinian cyst	1940, cured
7	Left salpingo-oophoritis; parametritis	Tuboovarian mass left fornix; thickening in right fornix	6 weeks. Returned 1 month. Right ovary cystic	6/28/35, liberation of adhesions; right oophorectomy	Left tube normal; left ovary adherent. Right tube normal; right ovary 4 inches in diameter	9/12/35, cured
8	Acute parametritis	Marked thickening in all fornices	2 weeks	12/29/36, ten months later for acute appendicitis; partial resection left tube aand ovary	Mild chronic salpingitis; corpora lutea of ovary	9/24/40, cured
9	Bilateral salpingitis pyosalpingitis	Clubbed right mass behind uterus in cul-de-sac. Left mass 1 inch in diameter	2½ months. Seemed to empty and refill	3/30/35, right salpingo-oophorectomy. Left salpingectomy	Bilateral hydrosalpingitis. Right cystic ovary	4/24/41, cured
10	Bilateral tuboovarian mass; fibroid uterus	Uterus hard; irregular; enlarged; fornices filled with hard masses	6/7/38, 2 months. Masses cleared	5/28/40, 2 years later operation. Supravaginal hysterectomy. Liberation of adhesions	Fibroid uterus; left tube and ovary necrotic; seat of abscesses	5/10/41, improved
11	Right oophoritis	Tender adherent right ovary	2 weeks 1 improved	7/11/39, 1 year later. Right oophorectomy; liberation of adhesions and appendectomy	Adhesions; cystic right ovary	10/24/40, cured

TABLE III A. FOR CLARIFICATION OF DIAGNOSIS IN PELVIC TUMEFACTIONS

NO.	DIAGNOSIS	IONTOPHORESIS	POSTTHERAPY FINDINGS	FINAL DIAGNOSIS	RESULT
1	Fibroid uterus; possible inflammatory mass	1 month	Uterus irregular; enlarged; hard; fibroid	Fibroid	None
2	Parametritis; probable nonsurgical fibroid; left salpingitis; bilateral oophoritis	5/5/39, 1 month	6/39, right ovary normal; left ovary prolapsed normal. Uterus normal. No evidence parametritis	Pelvic inflammatory disease	1/9/40, cured
3	Dextroretroverted uterus; probable fibroid uterus; coccygodynia	6/13/39, 1 month	Uterus normal; all fornices clear	Pelvic inflammatory disease	6/20/40, cured
4	Fibroid uterus; bilateral adnexal disease	9/11/37, 2 months	Right and left adnexal regions clear. Uterus in midline irregular, enlarged by fibroid in left cornu	Fibroid with pelvic inflammatory disease	12/4/37, improved
5	Parametritis; fibroid uterus	5/14/40, 1 month	All fornices clear; uterus normal	Pelvic inflammatory disease	10/15/40, cured
6	Possible fibroid, left parametritis	2/11/41, 1 month	Small fibroid 1 inch in diameter. Left cornu. All fornices clear	Fibroid with pelvic inflammatory disease	3/11/41, improved
7	Left parametritis; fibroid uterus	2/20/41, 1 month	Small sessile fibroid in left border of uterus. Fornices clear	Fibroid with pelvic inflammatory disease	3/25/41, improved
8	Fibroid uterus; cystic oophoritis	10/26/40, 3 weeks	All fornices clear; several small fibroids	Fibroid	3/18/41, none

TABLE III B. FOR CLARIFICATION DIAGNOSIS IN PELVIC TUMEFACTIONS (OPERATIVE CASES)

NO.	DIAGNOSIS	IONTO-PHORESIS	OPERATION	PATHOLOGY	RESULT
1	Fibroid uterus. Left salpingo-oophoritis	2½ months	7/14/36, Liberation of adhesions. Left ovary resected	Adhesions between intestine and ovary and left broad ligament. Corpus luteum cyst of ovary. Gigantic corpora fibrosa	4/1/37, unimproved
2	Fibroid uterus; bilateral salpingo-oophoritis. Cystic oophoritis	2 weeks	4/30/37, Both ovaries suspended; 2 small fibroids enucleated. Appendectomy	Uterus bound by adhesions to intestine and omentum; fibroid on postuterine wall; both ovaries normal. Tubes appear open	10/7/40, uterus retroverted, otherwise normal
3	Intraligament cyst; fibroid uterus	1 month	11/30/37, Myomectomy; appendectomy. 11/18/39, cesarean section	2 fibroids removed. Pregnancy	10/7/40, cured
4	Fibroid uterus; adhesions. Cystic right ovary	1 week	1939, Right oophorectomy	2 small fibroids; right papillocystadenoma; adhesions	
5	Possible fibroid uterus; right salpingo-oophoritis	1 month	2/16/37, Supravaginal hysterectomy; right salpingo-oophorectomy. Appendectomy	Right ovary cystic. Normal size	6/28/38, cured
6	Fibroid uterus	1 month	7/20/40, Supravaginal hysterectomy; appendectomy. Adnexa retained	Fibroid	3/8/41, cured
7	Fibroid uterus. Bilateral tuboovarian masses	2 months	9/27/40, Supravaginal hysterectomy. Partial removal of ovarian abscess. Liberation of adhesions	Fibroid uterus and left pyosalpingo-oophoritis	5/10/41, improved
8	Right tuboovarian mass; possible dermoid	1 month	6/13/39, Right oophorectomy	Right ovarian cyst 4 inches in diameter. Filled with fat and black hair	Cured
9	Carcinoma left adnexa and intestine. Exudate	19 days	10/31/36, Biopsy	Generalized adenocarcinoma	No change

TABLE IV. OVARIAN CYSTOMA

NO.	DIAGNOSIS	IONTOPHORESIS	FINDINGS	RESULT
		Nonoperated		
1	Third degree retroversion; enlarged cystic right ovary	10/20/36, 2 months	Uterus brought up. Right ovary normal	1/26/37, improved
2	Cystic cervicitis; bilateral cystic oophoritis	12/17/38, 4 months	Felt better. No physical change	9/21/40, unchanged
3	Left ovarian cyst. Parametritis	2/27/34, 1 month	Left ovary prolapsed. Normal	1/11/41, improved
4	Bilateral ovarian cystoma	11/4/39, 1 month	Left ovary normal; right ovary unchanged after 10 months	9/1/40, improved one ovary
5	Right ovarian cystoma	10/20/38, 6 weeks	Both ovaries normal	4/9/40, improved
6	Left ovarian cystoma. Retroverted uterus	1 week	Uterus brought up. Both ovaries normal	Improved
7	Left ovarian cystoma. Right parametritis	1/28/39, 2 weeks	Stopped treatment for 5 months. Returned. Cystoma increased in size	6/29/39, unchanged
8	Pelvic exudate; right cystic oophoritis	6/16/36, 3 months	Right ovary 1½ inches; cystic feel	1/30/40, pelvis normal. Improved
9	Left ovarian cystoma; retroverted uterus	9/1/38, 1 month	No change	9/22/38, unchanged
10	Bilateral cystic oophoritis	5/4/39, 2 weeks	Left ovary normal. Right slightly enlarged; returned 1 year later. Both ovaries normal	6/18/40, improved
11	Left ovarian cystoma; left parametritis	11/12/35, 1 week	Left ovary normal. Induration gone	10/13/39, improved
12	Right cystic oophoritis; right parametritis	2/1/41, 1 month	Pelvis normal; 2 months later pregnant	2/1/42, improved
13	Right cystic oophoritis; fibroid uterus	10/26/40, 2 weeks	Both ovaries normal; fibroid uterus	3/18/41, improved
		Operated		
14	Large right ovarian cystoma dermoid	1/13/39, 5 months	Dermoid. Right ovary removed	6/13/39, improved
15	Left ovarian cystoma; peri-oophoritis	5/19/38, 2 months	5/2/39, left ovary normal; returned 4 months later left ovary enlarged; operated for fibroid-ovary only 28 × 27 × 12 mm. Supravaginal hysterectomy and left oophorectomy	7/39/40, improved
16	Bilateral ovarian cystoma. Adhesions	10/8/35, 3 months	Left ovary normal (1/26/38); right slightly enlarged. Remained normal one year. Small cyst appeared in right fornix. One year later operated for left intraligament cyst	9/24/40, improved
17	Left ovarian cystoma; probable dermoid	4 months	9/27/40, left oophoritis	4/1/41, improved

of new growths were not altered, whereas the recessions noted all appeared to be located in areas of follicular cystic disease. The reason for such a recession is not clear, although the possibility that improved circulation may stimulate the continuance of cyclic changes in the cystic accumulations may be the factor responsible for the disappearance of these cysts.

Four patients were treated for collections of blood in the pelvis more or less encapsulated (Table V). In none of these was very much change produced. It appears that organized blood accumulations undergo slow resolution and absorption, practically unaffected by extraneous factors.

TABLE V. HEMATOMA, ENCAPSULATED EXUDATE, ETC. (4)

NO.	DIAGNOSIS	IONTOPHORESIS	RESULT
1	Probable pelvic hematocele following ectopic ruptured	3 months	Small cystic area left, immediately behind and to left of uterus
2	Left fornix exudate following hysterectomy	3 months	Mass grew large and more circumscribed with occasional bleeding per vaginam. Feels like a small piece of ovarian tissue
3	Left intraligamentous exudate	1 month	Mass almost gone. Returned 2 years later. Mass 3 inches in diameter; treated about 5 months. No change. Stopped treatment. Returned 5 years later. Pelvis clear
4	Probably organized hematoma between leaves of broad ligament	3 months	Mass only slightly affected

DYSMENORRHEA

It was noticed in the treatment of those patients with pelvic inflammation who concurrently suffered from dysmenorrhea that relief of the painful menstruation was coincident with the improvement in the

TABLE VI. DYSMENORRHEA (6)

NO.	DIAGNOSIS	IONTOPHORESIS	RESULT
1	Dysmenorrhea; sterility. Acutely anteflexed uterus	Through 2 periods	No effect
2	Dysmenorrhea	3 months	Pain decreased with each period, until third period, when was free of all pain
3	Dysmenorrhea; left salpingo-oophoritis	1 month	Pain, only slight
4	Dysmenorrhea; left salpingo-oophoritis	6 weeks	Pain gone; scant flow
5	Dysmenorrhea	1 month	No change. Subsequently operated for appendicitis. Now feels well
6	Dysmenorrhea	2 weeks	No relief

pelvic inflammatory disease. This observation led to the experimental treatment of dysmenorrhea in patients who were free from pelvic inflammation, and the results obtained are tabulated in Table VI. It is evident that when dysmenorrhea is caused by an associated pelvic inflammation, the pain is relieved as the pelvic inflammatory condition subsides. The results in patients with essential dysmenorrhea are too irregular to warrant the use of iontophoresis for its relief.

SUMMARY

As a result of nine years of experience with iontophoresis, we are convinced that the treatment is simple in application and practically free from any toxic reaction. Its greatest field of usefulness is in the treatment of inflammatory pelvic exudates. In such cases iontophoresis has made prolonged hospitalization unnecessary, has returned these women to usefulness, and has relieved symptoms much more quickly than is possible with other therapeutic methods. We now feel justified in stating that: (1) Mecholyl iontophoresis promptly cures exudative pelvic inflammation. (2) There is no effect on productive inflammatory pathology. (3) There is no effect on organized blood accumulations. (4) There is no effect on new growths, uterine, ovarian, or in other pelvic structures. (5) The therapy is a helpful differential diagnostic aid in pelvic masses. (6) Preliminary iontophoresis when associated inflammation exists renders operation easier and less extensive. (7) Certain follicular ovarian cysts are apparently influenced and disappear under therapy. (8) Dysmenorrhea associated with pelvic inflammation and caused thereby is relieved as the inflammation disappears, but primary or essential dysmenorrhea is unaffected in most instances.

From the foregoing, it is clear that iontophoresis is a safe, economic, rapid and practical therapeutic method for the relief of pelvic inflammation.

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EXPERIMENTALLY PRODUCED FIBROIDS IN THE GUINEA PIG AND THEIR POSSIBLE ANALOGY TO MYOMAS IN THE HUMAN BEING*

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FOR several years investigators have tried to produce uterine tumors in animals which could be compared to myomas in the human being.

In 1937 Nelson reported the production of fibromyoma-like nodules in the uteri of guinea pigs by prolonged administration of estrogens.

Moricard and Cauchoix produced fibromyomas in the female guinea pig by injection of estradiol benzoate. Lipschutz and Vargas have produced fibromalike abdominal tumors in guinea pigs by injection and implantation of estrogenic substances. They found that different estrogenic substances have a different growth-stimulating and tumor-promoting potentiality. They could increase the tumor-promoting action of estradiol in the guinea pig by esterifying it with certain acids, increasing its tumor-promoting potentiality up to 200 times by combining it with a certain isomer of caprylic acid. The uterine tissues not involved in the tumor formation were stimulated to a lesser degree to hyperplastic growth. The more continuously the estrogenic action was maintained, the more numerous and larger were the tumors produced. The longer the intervals between injections, the less tumor formation was obtained, no matter how great the potency of single injections. But even a relatively low level of estrogen stimulation was likely to produce tumors if it was maintained over a certain period of time, as by the implantation of pellets. No true parallelism was found to exist between the tumor-producing "tumorigenic" and the uterus-stimulating "hysterotrophic" action of different estrogenic principles.

The unpredictable tumor growth under the influence of estrogen on certain places within seemingly homologous tissues, and the dissimilar reaction of the surrounding tissues suggested that some less differentiated cells must be interspersed, which have a greater receptivity to growth stimulation. It is probable that these more responsive cells in the guinea pig are immature mesenchymal cells similar to those which Marchand and other investigators describe as "undifferentiated, perivascular, mesenchymal cells" persisting in the adult organism with the potencies of embryonic mesenchymal cells.

According to all investigators, it is more difficult and requires a much greater dosage of estrogen, to produce fibroids in guinea pigs in which the whole or a part of the ovarian tissue is retained, than it is in

*The estradiol dipropionate used in these experiments was donated by the Ciba Company.

spayed animals. The normal ovary of the guinea pig seems to contain substances which in some way modify and diminish the tumor-producing action of estrogen. It was also found that male guinea pigs have a relatively much greater resistance to the tumorigenic action of estrogen.

Lipschutz observed that the production of tumors by injection or implantation of estradiol could be prevented or arrested by simultaneous injection of progesterone in comparative dosage. Testosterone was found to be even more effective as a tumor-preventive, and the most potent was the cortical hormone, "desoxycorticosterone."

Perloff and Kurzrok produced a fibromyoma in one uterine horn of a guinea pig by implantation of an estradiol pellet. No fibroid was produced in the other uterine horn by implantation of an identical pellet when testosterone was simultaneously implanted.

Since 1937 we have been trying to produce fibromyomas in animals. Several series of rats were injected for several months with large doses of estrone. At the same time an attempt was made to produce a local irritation of the uterus by implantation of foreign bodies and of small pieces of various other tissues. Like other investigators, we were unable to produce any fibromyomas in rats. Attempts to produce fibromyomalike tumors in unspayed guinea pigs were also unsuccessful in our hands.

During 1940 we spayed a series of 110 guinea pigs and injected them three times weekly for four months with large doses of estradiol-dipropionate. Approximately 5 mg. were used for each animal on which the experiment could be completed. On account of the seemingly increased susceptibility to infection of the estradiol-injected animals, and unfavorable laboratory conditions, only 12 animals survived. However, all the surviving guinea pigs showed multiple intra-abdominal tumors of fibromyomalike character. The majority of these tumors originated from the uterus. In 10 of the guinea pigs the tumors were on the uterine horns, mostly apical and subserous. In 9 they were also in the uterine body. Aside from these, there were many tumors extragenital in location. The parietal peritoneum of the anterior abdominal wall was involved in 8. In 2 cases they were located on the diaphragm, and one of these had pushed up into the thorax. The viscera were not excluded and tumors were found on the bladder, spleen, pancreas, and ilium.

The varied locations of these tumors, with a predilection for the uterus, corresponded with the findings of other investigators. Generally the tumors were round or oval, had a firm, rubbery consistency, a smooth contour, and thinned-out capsule.

Microscopically all the tumors were of similar character. They consisted largely of intertwining bundles of fibrous tissue, running in all directions without any relation to any structural and anatomic unit. Between these fibrous strands were larger or smaller groups of muscle cells. These muscle cells were larger and thicker than the normal ones,

with a more granular cytoplasm. The nuclei were darker, larger, and more rounded.

In addition, there were occasional collections of fat and numerous round cells. In some places the pattern was very irregular and almost suggestive of sarcomatous changes. Mitotic figures were found frequently, but no invasion of the surrounding tissues was noted. Capillaries were present in abundance. The surface was usually composed of a capsule of flattened cells.

The question naturally arises: Is there any analogy between these experimental fibromyomas in guinea pigs and human myomas? We feel, with Lipschutz and Vargas, that these two types of tumors can be compared, in spite of their structural and biologic differences, when we make certain allowances for the dissimilar basic conditions under which the spontaneous and the artificial tumors are produced. One fact stands

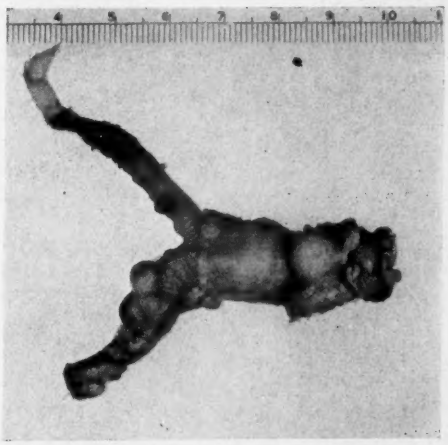

Fig. 1.—Multiple uterine tumors of guinea pig.

out which is valid for the etiology of all tumors: we cannot look for any single cause for their production; tumor growth is the result of a combination of favorable circumstances, the effect of the summation of various contributing factors.

Estrogenic substances, by being growth-stimulating, can become tumor-promoting if they can act in a certain quantity in sufficient intensity and over a certain period of time upon cells which are especially receptive; and if their action upon these cells is not balanced and neutralized by other protective substances.

In accordance with Lipschutz' observations, mentioned before, laboratory studies have shown that various natural and synthetic estrogenic substances affect different animal species in different degrees, and also different tissues of the same species in varying degrees. It is also known that several free and combined estrogenic fractions can be present in one organism at the same time, undergoing chemical changes from the

time of their production to the time of their excretion. They are esterified and neutralized by normal liver action and are excreted by the kidney. It can be assumed that these different fractions of the natural estrogens have also different effects on the various tissues of the organism in which they occur, and that some of their transitional phases may possess a relatively higher tumorigenic potentiality on receptive cells.

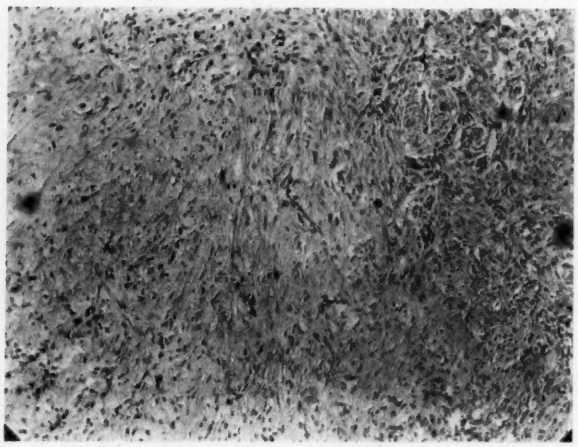

Fig. 2.—Section from medium-sized uterine tumor, low power.

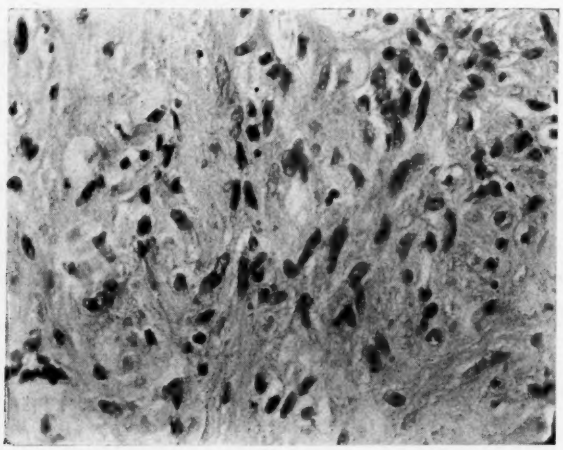

Fig. 3.—Section from medium-sized uterine tumor, high power.

There seems to be no direct chemical involvement of estrogen in the process of growth stimulation of myoma, in spite of its seemingly cumulative effect. But its action seems rather to be an indirect catalytic process. According to our own experiments there seems to be no storage of estrogen within the myomas. We made hormone assays of pieces of several human myomas and could not recover any appreciable amount

of estrogenic substances, as likewise we failed to recover any in the normal uterine muscle wall.

The most commonly accepted theory of the histogenesis of the uterine myoma in women is the one advanced by Robert Meyer who claims that the myoma originates from immature muscle cells. Meyer found small seedlings of muscle cells in certain uteri grouped in dense bundles from $\frac{1}{50}$ to $\frac{1}{5}$ mm. in diameter, which he interpreted as incipient myomas.

Common to all uterine muscle cells is a special growth energy, as manifested by their special physiologic response to the stimulus of pregnancy. This growth potentiality is greater on the fundus than on the cervix, and the part which is capable of greater hypertrophy during pregnancy shows also greater potency to tumor formation.

A growing myoma, like other tumors, seems to attract its own blood supply from the adjoining vessels, stimulating the proliferation of capillaries; vice versa, the rate of growth of a tumor is influenced and limited by the available blood supply. It is well known that myomas are likely to grow during physiologic and pathologic states of the uterus which are accompanied by hyperemia, as in pregnancy or in chronic pelvic inflammation; whereas they often retrogress during the temporary uterine involution of the puerperium and usually atrophy with the diminished blood supply of the menopause. It was also observed that occasionally myomas keep on growing after the menopause if they have an extrauterine blood supply by adhesions or by their atypical location.

Such observations have formerly led to the belief that the amount of blood supply was the basic factor controlling the growth of myoma.

In recent years it has been proved that the circulation of the uterus itself, and with it the circulation of the uterine myomas, is controlled to a great extent by hormonal action in synergism with the vegetative nervous system. It has been shown that estrin produces hyperemia of the uterus and that this circulatory trophic action is one phase of growth stimulation exerted by estrogen. The physiologic and pathologic conditions accompanied by hyperemia which seem to favor the growth of myoma are commonly associated with, or even partially produced by, increased or unbalanced estrogenic action.

A number of analogies are suggested when we compare experimental production of fibroids in guinea pigs with the spontaneous development of myoma in the human being. If we follow up these analogies and compare the sequence of experimental steps with the variety of factors thought responsible for the development of the human myoma, we may be enabled to fill in the gaps between various seemingly unconnected factors involved in the genesis of myoma. Some of these analogies seem to fit in readily with certain known clinical facts.

For example, corresponding to the production of experimental fibroids, it seems plausible that human myomas are more likely to be produced

when there is a persistence of a comparatively even level of estrogen than when the estrogen fluctuates in normal cycles. In practice we find such conditions of protracted estrin stimulation in the presence of follicular retention cysts, which Witherspoon considers a primary cause of myoma. Following up the inference suggested by the experiments, persistence of even a moderate degree of estrin stimulation could more likely lead to myoma formation if it were accompanied by other ovarian or co-ordinated endocrine deficiencies. In such a case the estrogenic action would not be counterbalanced by other endocrine catalysts. Lack of endocrine equilibrium with a relative preponderance of certain estrogenic fractions could also explain the common association of sterility with myoma. Favoring such an occurrence would be the abundance of easily stimulated immature muscle elements in an underdeveloped uterus.

SUMMARY AND CONCLUSIONS

Lipschutz and several other investigators have produced fibromyomatous tumors in guinea pigs by protracted use of estrogenic substances. Retention of normal ovarian tissue or the simultaneous use of certain other endocrines inhibited the tumor formation. In our own experiments we were able to produce similar tumors in guinea pigs. In spite of histologic differences, certain analogies can be found between the genesis and production of experimental fibroids and human myomas. Both types of tumors originate from mesoblastic cells, the guinea pig fibroids seemingly from undifferentiated connective tissue cells, the human myomas from immature muscle cells. The growth of both tumors seems to depend upon estrogenic action when this is not counterbalanced by other growth-controlling catalysts.

By following up the apparent analogies between the data found in the experimental production of fibroids with the diverse factors thought responsible for the genesis of human myomas, we possibly can correlate some of these factors and come closer to an understanding of the etiology of myoma.

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CLINICAL OBSERVATIONS IN TREATMENT OF NAUSEA AND VOMITING IN PREGNANCY WITH VITAMINS B_1 AND B_6

A Preliminary Report

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PERNICIOUS vomiting of pregnancy has long been a nemesis to the physician practicing obstetrics as well as to the unfortunate patient. Relief has often been obtained from liver injections as well as from hospitalization with attendant intravenous glucose infusions, a method often having the disadvantage of being both slow and expensive. Vitamin B_1 has more recently been introduced into this field with some success; but here again the persistent case of hyperemesis gravidarum has not responded with entire satisfaction.

Herewith is reported an experience with the use of vitamin B_6 in what is believed to be a new therapy for this condition. This treatment is recommended, because it seems more effective and is simpler to administer.

In May, 1941, vitamin B_6 was administered to an obstetric patient, Mrs. M. Mrs. M. had intelligently cooperated in every trial of a remedy and had completely failed to respond to any treatment. Since she had been similarly incapacitated with her first pregnancy, she concurred in a desire to try the results of vitamin B_6. An intravenous injection of 2 c.c. (20 mg.) was made and the patient was told to report results. Four days later she returned with the story of having been able to retain her evening meal on the day of the injection, and

TABLE I. CLINICAL OBSERVATIONS

PATIENT	NO. MG. GIVEN	DOSAGE	RESULT
		Vitamin B_1	
D. B.	150	Three 50 mg. injections over a period of 1 week	Complete relief of nausea
W. B.	620	25 to 50 mg. injections over period of 2 to 7 days	Nausea and vomiting
H. C.	100	Two 50 mg. injections over period of one month	Relief the first month. Repeated second. No recurrence
H. C.	350	50 and 100 mg. doses at week intervals	Usually relieved in about four days
J. D.	100	1 dose	Vomiting cleared. Nausea not marked thereafter
E. D.	200	Two 50 mg. injections at two-day intervals	Relief for 48 hours
		Four 25 mg. injections at six-day intervals	No vomiting. Nausea relieved in four days
J. D.	50	1 dose	Immediate relief
M. D.	250	Ten 25 mg. injections intravenously	Temporary relief after each dose for three or four days
H. D.	100	Four 25 mg. injections	Nausea and vomiting relieved in three or four days
M. E.	100	Four 25 mg. injections at week intervals	Greatly improved in three days
C. E.	25	1 dose intravenously	Marked improvement
W. F.	150	Three 50 mg. injections	Vomiting ceased
J. F.	50	1 dose intramuscularly	Relieved entirely
L. F.	250	One 100 mg. injection	Relieved. Nausea returned in two weeks
		25 and 50 mg. injections	Relief for a week after each injection
E. G.	100	50 mg. injections at two-week intervals	Relieved
L. J.	25	1 dose	Complete relief
L. G.	250	Five 50 mg. injections intramuscularly from 4 to 5 days apart	Relieved after each injection
S. H.	150	Two 50 mg. injections Two 25 mg. injections	No relief
T. H.	100	Two 50 mg. injections over period of 8 days	Relieved entirely after second dose
P. I.	200	One 100 mg. injection Two 50 mg. injections	Improved but not completely Relieved vomiting
G. J.	300	Three 100 mg. injections at wide intervals	Coincided periods of depression. Moderate temporary relief
B. K.	125	25 and 50 mg. injections at week intervals	Good results. Last dose given for fatigue

TABLE I—CONT'D

PATIENT	NO. MG. GIVEN	DOSAGE	RESULT
J. L.	275	25 mg. injections at one-week intervals	Temporary four-day relief
W. L.	600	25 mg. injections	No relief given account limited diet to keep up concentration B_1. Weight kept up fairly well, ceased after 2 units crude liver given. One 300 c.c. blood transfusion for proteins
W. M.	25	1 dose intravenously	Relief
R. M.	150	Three 50 mg. injections	Acute cold after taking
G. M.	200	One 100 mg. injection Two 50 mg. injections 1 day interval	Neuritis in arm and nausea Moderate relief of nausea
M. N.	50	Two 25 mg. doses	Immediate relief after each dose. No further injections needed
R. P.	75	25 and 50 mg. doses	Relief marked but not complete
J. R.	275	25 and 50 mg. injections given at three-day intervals, then weekly	Vomiting ceased
D. R.	900	25 and 50 mg. injections every 3 or 4 days	Became nauseated if discontinued
G. S.	50	1 injection	Relief from vomiting. Moderate nausea
B. S.	300	Six 50 mg. injections	Relief for 5 or 6 days
L. S.	25	1 dose intravenously	No result
N. S.	250	Five 50 mg. injections given every 4 days	Vomiting ceased and nausea moderated
S. S.	75	25 and 50 mg. doses	Improved
N. S.	825	25 and 50 mg. doses given every 2 or 3 days	Temporary relief for 1 to 2 days. Nausea returned if discontinued injections
S. S.	125	One 100 and one 25 mg. injection	Improved after first injection
J. S.	100	1 injection	Improved
N. T.	100	Two 50 mg. injections	No improvement
L. W.	350	Seven 50 mg. injections at weekly intervals	Temporary relief of nausea after each injection
H. W.	25	1 dose intravenously	No improvement
E. W.	100	Two 50 mg. doses one week apart	Relieved nausea and severe vomiting
R. W.	600	10 mg. daily intravenously over a period of 2 months	Immediate improvement with recurrence when discontinued

TABLE I—CONT'D

PATIENT	NO. MG. GIVEN	DOSAGE	RESULT
		Vitamin B_6	
C.	1000	Twenty 50 mg. injections	Vomits occasionally
R.	1250	Twenty-five 50 mg. injections	Vomits some but not confined to bed
S.	1500	Thirty 50 mg. injections given tri-weekly for 3 weeks. Discontinued and vomiting returned. Began again tri-weekly	Was well as long as B_6 was given
L.	750	Fifteen 50 mg. injections	Much improved
H.	500	Ten 50 mg. injections	Improvement
P.	150	Three 50 mg. injections	Relieved
T.	150	Three 50 mg. injections	Much improved
B. K.	100	Two 50 mg. injections intravenously on successive days	Excellent results
R. H.	100	Two 50 mg. injections intravenously 5 days apart	Good results
R. B.	250	Five 50 mg. injections intravenously from one- to five-day intervals	75% improvement
G. R.	400	Eight 50 mg. injections intravenously from 1 to 5 days apart	75% improvement
L. K.	100	Two 50 mg. injections intravenously on successive days	Complete relief
W. J.	100	Two 50 mg. injections intravenously 1 day apart	Excellent results
R. E.	150	Three 50 mg. injections on successive days. Given intravenously	Excellent results
J. McC.	200	Four 50 mg. injections intravenously on successive days	About 50% improvement by fourth dose
D. D.	250	Five 50 mg. injections	Relief from vomiting. Slight nausea
H. C.	125	Three injections given from two- to five-day intervals	Excellent results
D. H.	450	Nine 50 mg. injections twice weekly	Good results
S. D.	250	Five 50 mg. injections twice weekly	Excellent results
D. F.	100	Two 50 mg. injections one week apart	Improvement
S. G.	200	Four 50 mg. injections twice weekly	Complete relief
R. H.	400	Eight 50 mg. injections intravenously tri-weekly	Excellent results

TABLE I—CONT'D

PATIENT	NO. MG. GIVEN	DOSAGE	RESULT
H. H.	300	Six 50 mg. injections three days apart	Complete relief of vomiting. No nausea after last injection
L. S.	150	Three 50 mg. injections	No improvement
J. M.	100	Two 50 mg. injections	Good results
J. N.	200	Four 50 mg. injections intravenously	Excellent results
R. S.	150	Three 50 mg. injections	Complete relief
F. S.	250	Two 50 mg. injections intramuscularly	No relief
		Three 50 mg. injections intravenously	Partial relief
R. P.	300	Six 50 mg. injections intravenously 2 days apart	Relief after second injection
M. A. (10 wk. gestation)	150	Three 50 mg. injections	Complete relief of vomiting. No nausea for 3 days after each injection. Able to continue office work
A. K.	300	Six 50 mg. injections	Partial relief after first dose. No nausea after last injection
G. S.	50	One 50 mg. injection	Improved
R. G.	250 (B_6)	50 mg. injections intravenously daily	*No improvement whatsoever*
	375 (B_1)	50 mg. injections intravenously daily	No improvement. Nausea, vomiting, and ptyalism continued
H. B.	150	Three 50 mg. injections	Relief from slight nausea. Patient had complained bitterly of a migraine. *Migraine was relieved*
J. S.	50	One 50 mg. injection	Patient had no nausea but had a migraine for 2 weeks. Migraine relieved for 48 hours after injection
C. B.	50	One 50 mg. injection	Complete relief
R. P.	50	One 50 mg. injection	Relief of vomiting. Slight nausea

of having been almost entirely free of nausea until the fourth day. She came in to ask for another dose. The injections were repeated until five doses were administered. Following these injections, she had no return of nausea or vomiting.

This experiment led to the use of similar treatment for Mrs. McM., a patient of the same type. She responded as quickly and as completely as the first case. Thereafter this vitamin was made a routine treatment in cases of vomiting of pregnancy. Apparently, it was con-

cluded, vitamin B_6 is the most efficient therapeutic agent in nausea and vomiting of pregnancy so far tried. It has the added advantage of being practical for office use as well as economical.

Results of these treatments were passed on to the Obstetrical Staff at Baylor University College of Medicine. To date, vitamins B_1 and B_6 have been administered by different members of the Staff. A report of the clinical observations was made to the regular monthly staff meeting of Baylor Hospital on Jan. 22, 1942.

It has been repeatedly observed that the deliberate ingestion of food materially lessens the early nausea and vomiting in pregnancy. With this thought in mind, we have attempted to create a desire for food by the administration of vitamin B_1 or B_6 to all patients who complained of any degree of nausea and vomiting in the first trimester of pregnancy.

George R. Cowgill (*Am. J. Physiol.* 57: 1921) published a paper, "A Contribution to the Study of the Relation Between Vitamin B and the Nutrition of the Dog." Itemizing experiments on the hunger of dogs and verifying a report published by Karr in 1920, he drew this conclusion: "The observation of Karr, 'that some relationship exists in the dog between the desire to partake of food and the amount of the so-called water-soluble vitamine ingested,' has been confirmed." To the list of substances reported by Karr, Cowgill added alcoholic extracts of wheat embryo, rice polishings, and navy bean, and made the following statement: "All of the products were tested and found to restore appetite or to relieve polyneuritic symptoms."

Again, Cowgill and co-workers (*Am. J. Physiol.* 77: 1926) on the subject, "Studies in the Physiology of Vitamins," published an article on "Vitamin B in Relation to Gastric Motility." Among the conclusions of this paper he states: "It is difficult to decide whether or not vitamin B maintains the desire to eat simply by aiding in the preservation of the normal gastric tone. The marked systemic manifestations characteristic of advanced cases of vitamin B deficiency suggest that the loss of the desire to eat in such cases is due as much to a generalized systemic disturbance as it is to an abnormal condition localized in the alimentary canal."

Further, in October, 1937, Dr. Charles Martin, Professor of Radiology, Baylor University College of Medicine, in a preliminary report on "The Treatment of Roentgen Sickness With Synthetic Vitamin B_1 Hydrochloride," states in his conclusions: "Vitamin B_1 is an effective drug for the treatment of roentgen sickness. It is harmless and produces no complicating symptoms."

Since roentgen sickness is many times characterized by extreme nausea and pronounced vomiting similar to the nausea and vomiting of pregnancy, we began to administer first vitamin B_1 and later vitamin B_6 as a therapeutic measure for these symptoms in pregnancy.

SUMMARY AND CONCLUSIONS

1. Almost complete relief from nausea and vomiting of pregnancy was gained by administering vitamins B_1 and B_6 in a varying dosage

at irregular intervals and by either the intramuscular or intravenous route.

2. Relief from nausea and vomiting occurred more often and more completely with the use of vitamin B_6 than with vitamin B_1.

3. Many patients returned for injections only when nausea and vomiting reappeared.

4. No undesirable reactions were noted.

5. Two patients were relieved of an accompanying migraine.

6. This vitamin should be investigated as to its effect on vomiting due to other drugs, such as morphine, sulfanilamide, etc.

1529 MEDICAL ARTS BUILDING

VITAMIN E AND PREMATURE LABOR

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INTRODUCTION

PREMATURITY per se is recognized as the greatest single cause of stillbirths and neonatal deaths. There is no need to cite the actual statistics on this enormous wastage of infant life. Moreover, a peculiar sterility pervades medical papers dealing with its prophylaxis. Such clichés as "better prenatal and pediatric care," "adequate rest" and "a nourishing diet" appear in them all too frequently—remarks which are singularly unhelpful and imply a too casual approach to the study of this situation. Baird and Wyper[1] point out: "Among booked cases only slight improvement in the infant death-rate can be looked for by improvement in treatment along the present lines. The big factors are the toxemias—unexplained premature labor, and unexplained death."

It was suggested in 1937[2] that premature labor might be due to the same pathologic endocrine background responsible for spontaneous abortion and that vitamin E should be as valuable in the prevention of premature delivery as in the prevention of abortion.

Kotz, Parker and Kaufman[3] also have concluded that probably the same factors causing bleeding in early pregnancy are responsible for the onset of premature labor, and that the etiology of the latter is, therefore, to be sought in the endocrine constitution of the mother. They gave their patients of this type a combination of vitamin E, thyroid extract, and progesterone until term.

I desire to present here a detailed report of my results in private practice when using only vitamin E for 46 threatened premature deliveries.

TABLE I

CASE	STAGE OF PREGNANCY IN WEEKS	SYMPTOMS		PREVIOUS OBSTETRIC HISTORY*	BLOOD ESTRIN4*	THERAPY* (DAILY)	RESULTS
		PAINS	BLEEDING				
1	31	+	0	1 term child after toxemic pregnancy; one normal term pregnancy	Neg. at 30 weeks	0	
	37	+	+ (spots)			℥ii w.g.o.	8 lb. normal term boy
2	28	+ (labor pains)	0	0	Neg. at 28 weeks	℥iv w.g.o.	
	34	+				Off w.g.o. for 4 days before	5½ lb. premature normal girl
3	32	+	+ (spots)	Stillborn (toxemic) at term	Pos. at 8 weeks	℥ii w.g.o.	
	33	+	+ (spots)			Exam. shows no previa	
	34	+	+ (moderate bleeding)	0			
	37	0	+ (spots)				
	38	0	+ (spots)				6 lb. 7 oz. normal term girl
3 (a)	32	+	0	1 term stillborn, 1 normal term child	Pos. at 6 weeks	℥iv w.g.o.	7 lb. 4 oz. normal term boy
4	28	+	0	1 spont. ab.; many threats this pregnancy	Pos. at 5 weeks	℥ii w.g.o. and bed	
	32	+	0				
	34	Spont. rupt. membranes	0				5 lb. normal premature girl
5	28	+	0	1 toxic pregnancy with normal term child	Pos. at 13 weeks	℥i w.g.o.	
	32	+ (labor pains for 12 hours)	0				
	34	0	+ (mod.)				
	36	0	+ (spots)				Normal term child
6	37	+ (spont. rupt. membranes)	0	0	Pos. at 24 weeks	℥i w.g.o.	5 lb. 7 oz. normal premature boy

*w.g.o., wheat germ oil; pos., positive; neg., negative; spont. ab., spontaneous abortion.

TABLE I—CONT'D

CASE	STAGE OF PREGNANCY IN WEEKS	SYMPTOMS		PREVIOUS OBSTETRIC HISTORY*	BLOOD ESTRIN4*	THERAPY* (DAILY)	RESULTS
		PAINS	BLEEDING				
7	34	0	0	1 spont. ab., many threats this preg.	Pos. at 28 weeks	6 mg. ephynal	7½ months macerated fetus delivered by induction
8	34	0	+ (spots)	1 normal term child (toxemic after sixth month)	Pos. at 26 weeks	℥ii w.g.o.	8 lb. normal term girl
9	28	+	+ (brisk)	1 term child and 1 term mongolian	Pos. at 10 weeks	℥iv w.g.o.	Normal premature, lived 4 hours
10	34	+	0	2 term children with toxemia first preg. and threatened ab. in both	Pos. at 12 weeks	36 mg. ephynal	10 lb. normal term boy
11	34	+ (labor pains 4 hr.)	0	1 normal pregnancy	Neg. at 7 weeks	℥ii w.g.o.	8 lb. normal term child
12	34	+ (to hosp. ready for delivery)	0	0	Pos. at 34 weeks	℥iv w.g.o.	7 lb. 6 oz. normal term child
13	28	+ (severe)	+ (spots nearly every day)	0	Pos. at 10 weeks	℥iv w.g.o.	
	32	+	+ (spots)				7 lb. 6 oz. normal term child
14	34	+	0	1 normal term child	Pos. at 11 weeks	℥i w.g.o.	6 lb. 6 oz. normal boy
15	35	+	0	1 term child with harelip and cleft palate	Pos. at 9 weeks	℥ii w.g.o.	
	38	+ (crying with pains)	0				7 lb. normal term girl
15 (a)	33	+	0	1 deformed and one normal child	Neg. at 3 weeks	℥vi w.g.o.	7 lb. normal term boy
15 (b)	32	+	0	1 deformed and two normal children	Not done	℥i w.g.o.	
	36	+ (labor pains nearly every day)	0				6 lb. 4 oz. normal term boy

TABLE I—CONT'D

CASE	STAGE OF PREGNANCY IN WEEKS	SYMPTOMS		PREVIOUS OBSTETRIC HISTORY*	BLOOD ESTRIN[4]*	THERAPY* (DAILY)	RESULTS
		PAINS	BLEEDING				
16	32	+	0	2 normal term children	Neg. at 17 weeks	℥i w.g.o.	
	33	+	0			℥iv w.g.o.	9 lb. 7 oz. term boy with bad cleft palate, harelip and bloody amniotic fluid
17	29	+	0	0	Neg. at 8 weeks	℥vi w.g.o.	
	36	+ (labor pains for 6 hr. after husband lost overseas)					7 lb. 6 oz. normal term boy
18	32	+	+ (moderate)	0	Pos. at 3 weeks	℥lss w.g.o.	6 lb. 6 oz. normal term girl
19	28	0	+ (moderate for 3 days)	1 term child and 1 spont. ab. Many bleedings this preg.	Not done	℥lss w.g.o.	8 lb. 4 oz. normal term boy
20	29	+	0	2 normal children	Pos. at 5 weeks	℥vi w.g.o.	
	31	+	0			℥i w.g.o. and bed	7 lb. 4 oz. term girl. It died at 2½ mo. after operation revealed complete absence of bile duct
21	36	+ (active)	+ (moderate for 6 days)	0	Pos. at 27 weeks	℥i w.g.o.	7 lb. normal term child
22	28	0	+ (spots)	0	Pos. at 24 weeks	℥ii w.g.o.	
	31	0	+ (spots every day for 2 weeks)			℥iv w.g.o.	
	32	0	Moderate bleeding			Exam. for previa neg. so ℥i w.g.o. begun. Bad pyelitis developed	Stillborn normal breech at 36 weeks

TABLE I—CONT'D

CASE	STAGE OF PREGNANCY IN WEEKS	SYMPTOMS		PREVIOUS OBSTETRIC HISTORY*	BLOOD ESTRIN4*	THERAPY* (DAILY)	RESULTS
		PAINS	BLEEDING				
23	31	0	+ (spots)	1 spont. ab.	Pos. at 14 weeks	3iv w.g.o.	7 lb. 10 oz. normal term boy
23 (a)	34	+	0	1 spont. ab. and 1 term child	Pos. at 8 weeks	3ii w.g.o.	8 lb. normal term girl
24	28	Spont. rupt. membranes	0	1 spont. ab. Many threats this preg.	Not done	℥i w.g.o.	
	33	+	+ (brisk bleeding)				Anencephalus with clubfeet at 33 weeks
25	33	+	0	0	Pos. at 8 weeks	3iv w.g.o.	7 lb. 8 oz. normal term stillborn due to prolapsed cord in breech presentation
	37	+ strong	0				
25 (a)	31	+	0	1 term stillbirth	Neg. at 5 weeks	3vi w.g.o.	8 lb. normal term boy
26	32	+	0	Ectopic and one term child	Not done	3vi w.g.o.	
	36	+ (severe)	0				7 lb. 8 oz. normal term girl
	37	+ (severe)	0				
27	35	+	0	0	Pos. at 4 weeks	℥i w.g.o.	Macerated premature male 3 lb. 4 oz.
28	36	0	+ (spots)	0	Neg. at 18 weeks	3ii w.g.o.	7 lb. normal term girl
29	30	+	+ (spots)	0	Pos. at 26 weeks	3iv w.g.o. Then extra doses for one day. Rupt. membranes. 3iv w.g.o. q.i.d. and b.i.d. After 3 days went into labor	Premature twins of 2 lb. 12 oz. and 2 lb. 5 oz. Lived 2-6 hours only
30	37	0	+ (spots)	1 term sp. bifida	Pos. at 14 weeks	Ephynal mg. 30	8 lb. 8 oz. normal term boy
31	29	+	0	1 term child	Pos. at 10 weeks	3iv w.g.o. up to 3viii w.g.o.	
	30	to hospital for "labor"					9 lb. normal term girl
32	38	+	+ (gush)	0	Neg. at 4 weeks	3i w.g.o.	
					Neg. at 18 weeks		8 lb. 8 oz. normal term boy

TABLE I—CONT'D

CASE	STAGE OF PREGNANCY IN WEEKS	SYMPTOMS		PREVIOUS OBSTETRIC HISTORY*	BLOOD ESTRIN[4]*	THERAPY* (DAILY)	RESULTS
		PAINS	BLEEDING				
33	30	0	+ (brisk bleeding)	2 normal term children	Pos. at 26 weeks	℥i w.g.o.	7 lb. normal term girl. Placenta immediately after baby
34	36 38	+ typical labor pains	0 0	6½ months spont. miscarriage	Pos. at 10 weeks	℥i w.g.o. up to 30 mg. ephynal	8 lb. normal term boy
35	32 36	+ + (labor pains)	0 0	1 toxic term preg.	Not done	3i w.g.o. 9 mg. ephynal and 3iv w.g.o.	8 lb. normal term boy
36	31	+	0	5 weeks spont. ab.	Pos. at 4 weeks	Ephynal mg. 10 per day	Macerated premature twins at 7 months
37	28 36	0 + (strong labor pains)	+ (spots) 0	1 normal term child	Pos. at 4 weeks	30-50 mg. of ephynal 75-125 mg. of ephynal	Normal term 7 lb. 2 oz. boy with typical abruptio type of placenta
38	30 31 34	+ + +	+ (spots) 0 + (spots)	1 eclampsia (postpartum) 1 normal term child 1 abortion 1 toxic preg. at term	Not done	3iv w.g.o. ℥i w.g.o. ℥iss w.g.o.	7 lb. normal term child
39	28 34	+ +	0 0	0	Neg. at 3 weeks	3i w.g.o. ℥i w.g.o.	7 lb. normal term boy
40	31 33 34 38	+ + + (severe) +	0 + (spots) 0 0	0	Pos. at 12 weeks	30 mg. ephynal 40 mg. ephynal 50 mg. ephynal henceforth	7 lb. 3 oz. normal term boy
41	35	+	0	0	Pos. at 19 weeks	3ii w.g.o.	Premature 4 lb. 9 oz. female (extrocardia), lived one day

DISCUSSION

It is whipping a straw horse to repeat[5] that premature expulsion of the fetus at any stage of pregnancy may be due to more than one single cause, viz., deficiency of vitamin E. But there are etiologic factors of

the first importance and many of very minor significance; disturbance of the estrogen: vitamin E equilibrium[6] appears to be the most important of the primary causes. This is illustrated by the fact that estrogen excess was discovered very early in 73 per cent of the 40 of these 46 pregnancies tested for it and also by the success of vitamin E in preserving so many of these precarious gestations. It is felt very strongly that even more of these pregnancies could have been preserved had larger doses of vitamin E been used prophylactically. Our results have improved greatly as we have moved in this direction.

Many women experience several threats to the integrity of a pregnancy between its beginning and term. It is probably safe to assume that much the same cause is operative each time. It is important, therefore, that the status of each pregnant woman should be studied as early as possible and that if such a prophylactic measure as the administration of vitamin E is indicated, it should be instituted at once. It is just as important, but more often overlooked, that E-therapy should be maintained until delivery at term. It should no longer be necessary to insist that only potent preparations of vitamin E should be used, the best being a fresh refrigerated bulk wheat germ oil or a synthetic alpha-tocopherol. Many of the products on the market are so unsatisfactory that it is no wonder that E-therapy lies under a cloud at the moment.

Sometimes the first clinical inkling of premature delivery, however, is a sudden rupture of the membranes. This almost inevitably spells labor, although we have seen pregnancy continue for weeks and months thereafter in four women (one being Case 24) to whom this happened and who were promptly given huge doses of vitamin E. It is desirable, therefore, that such a danger should be foreseen, if possible; for that reason, I test the blood estrin[4] of each pregnant woman at her first antenatal visit. The table illustrates in part how useful this test has proved. It has been seriously criticized,[7, 8] although something has been said in its defense[9, 10] too. Its clinical utility in our hands is beyond doubt. For example, 73 per cent of the patients tested revealed estrogen excess and 76 per cent were taken to term with the delivery of living children after the administration of vitamin E. These figures are scarcely a coincidence. It is suggested that either it or an alternative method of assay is a sine qua non in the prophylaxis of prematurity.

Much more bleeding can occur in late than in early pregnancy without unduly jeopardizing its integrity. Probably this is due to the greater proportion of adequately adherent placenta that remains undisturbed in the former. It could be anticipated, therefore, that late pregnancies would be more easily preserved than early ones, and that is our experience.

Twenty-seven of these 41 women had had one or more previous pregnancies. Sixty-one per cent of these 38 previous pregnancies had ended in toxemias, monstrosity, stillbirth, or in abortion or some such premature expulsion of the fetus. This falls in line with Young's conception of the "abortion sequence."[11] If the patient is able to avoid the Scylla of abortion or miscarriage she exposes herself to the Charybdis of prematurity, toxemia, or monstrosity. This sequence of dangers can be suspected before pregnancy if she is a hypothyroid and in the earliest weeks of pregnancy if she has an elevated blood estrogen level. Many scores of times the estrogen assay has foretold trouble months before it was detectable clinically.

The dose of vitamin E required to preserve a precarious pregnancy in "normal" condition rises gradually toward term, which could be inferred from the fact that E insures proper placentation;[12] more should be needed as the placenta enlarges. It is not surprising, therefore, that very large doses of wheat germ oil or synthetic alpha-tocopherol acetate were needed to prevent premature delivery in many of the women cited in the table.

The wisdom of attempting to preserve these unsettled pregnancies has often been questioned. The writer has repeatedly[13-15] urged that it was worth while, and Falls[16] has recently supported this view. Certainly, only 3 of the 41 live children secured in this series were defectives (7 per cent). The anomalies delivered were a cleft palate and hairlip, a congenital bile duct obliteration, an anencephalus with clubfeet, and an extrocardia, but only one of these could and did live as long as three months. One must weigh his misfortune against the potential value of the lives of the other 38 children preserved either by Nature or vitamin E or both. The choice before the attending obstetrician, as seen in this light, seems obvious.

Doubtless some of these threats of premature delivery would have subsided without any treatment. But I have watched every one of these anxiously and carefully and am inclined to ascribe their outcome more to vitamin E than fate. The series is uncontrolled, but obstetricians have been watching untreated series of these cases for too many decades. The poor results of expectant treatment are only too well known.

SUMMARY

1. A series of 46 cases of threatened premature labor is presented. A blood test for imbalance between estrogens and vitamin E was done on 40 of these pregnant women when first seen. Seventy-three per cent revealed estrogen excess.

2. All were treated prophylactically, or at the time of the threat, with vitamin E. Where E is indicated in any precarious pregnancy, it should be given in gradually increasing dosage until term.

3. Seventy-six per cent of the 46 patients were taken to term with the delivery of live children.

4. Seven per cent of the 41 live children delivered were defectives, but only one of these could and did live three months or longer.

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MORTALITY OF PREMATURELY BORN INFANTS

Influence of Certain Antenatal and Postnatal Factors

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THE mortality rate of prematurely born infants is many times as great as that for full-term children. The chief factor which leads to this inordinate fatality is the imperfect development of the small baby and its inability to cope successfully with an extrauterine environment. Any attack upon the problem must consider not only the actual care of the premature infant but also the maternal or other factors which induced or necessitated the early termination of pregnancy. This study was undertaken to explore some of these factors as they appear in the children born in a state-operated general hospital catering largely (95 per cent) to the indigent population of an essentially rural district.

Any child weighing less than 2,500 Gm. at birth was considered prematurely born, irrespective of other anthropometric data or of the maternal menstrual history. Between July 1, 1926, and June 30, 1941, 861 infants weighing from 700* to 2,499 Gm., among 14,594 born to 14,437 women, were included in this category, a prematurity incidence of 5.9 per cent. There were 27 pairs of twins with one child and 34 with

*700 Gm. was selected as the lower level because no children weighing less and born alive in this Clinic have survived.

both children premature by definition. The 861 infants were therefore born to 827 mothers. The mothers of 347 children were primigravidas (40.3 per cent). All but 18 of the women were white. The majority of the patients were indigent (783), married (702), and adherents to the protestant religions (626). Forty-one women were syphilitic (5.0 per cent).

During the years 1926 to 1935, the premature children were housed in the regular nursery where there was one old-model incubator. Thermostatic regulation served to keep the temperature between 75° and 80° F., while heat cradles were available to supplement the single incubator. No attention was paid to the humidity of the air. Fresh breast milk was frequently available from ward patients. An isolation nursery was in use. During the last six years covered by the report, all children under 2,500 Gm. in weight were cared for in a special nursery without cubicles. The temperature was hand regulated and an attempt was made to keep the room at 85° F. A relative humidity of approximately 50 per cent was maintained by a simple, hot-water spray humidifier. Frozen breast milk was available to supplement that obtained directly from nursing women. Gauze masks were worn by all attendants from 1930 to 1935, inclusive, but not during the other intervals. During the entire 15 years the nurseries were under the control of the obstetric staff but excellent pediatric consultation was always available and was frequently requested.

Fetal and Infant Mortality.—There were 165 (19.2 per cent) stillbirths and 153 (17.7 per cent) infants who died before discharge from the hospital, leaving 543 (63.1 per cent), who were dismissed alive. Through the assistance of the Division of Vital Statistics of the Iowa State Department of Health, it was learned that at least 36 of those discharged alive died before the end of the first year. This postneonatal mortality rate (66 per 1000) is higher than would have been expected among an equal number of term children. The total salvage at the end of twelve months was approximately 58.9 per cent, whereas 70.5 per cent of the prematures from twin births survived. The greatest neonatal mortality was during the first day when 108 (71.4 per cent) of the 153 deaths occurred. Only 21 died after the first week, exclusive of those who died after the first month.

In the five and one-half years after the introduction of air humidifiers in the nursery (1936 to 1941), there were 447 prematurely born children with 297 survivors (66.4 per cent), in contrast to the 414 born in the preceding nine and one-half years with 246 survivors (59.3 per cent).

Masking was in vogue for six years (1930 to 1935, inclusive) during which there were 347 premature infants with 207 survivors (59.1 per cent), as compared with 514 and 336 survivors (65.3 per cent) in the other nine years when masks were not worn. Upon comparing the earlier period (1926 to 1929) when there was no masking and no humidification and the most recent period (1936 to 1941) when masking was not employed but humidity control was exercised, the mortality rates are 53.3 and 66.4 per cent, respectively.

TABLE I. INCIDENCE OF PREMATURELY BORN AND SURVIVING BABIES, STILLBIRTHS, AND DEATHS DURING THE FIRST MONTH OF LIFE CALCULATED BY YEAR

YEAR	NUMBER OF PREMATURES	TOTAL NO. OF BABIES BORN	INCIDENCE OF PREMATURES PER CENT	PER CENT OF PREMATURES—BY YEAR					
				GRADUATED ALIVE		STILLBORN		DIED FIRST MONTH	
				CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
26 (6 mo.)	6	104	5.8	4	66.7	2	33.3	0	00.0
27	19	250	7.6	12	63.1	2	10.5	5	26.3
28	19	256	7.4	12	63.1	2	10.5	5	26.3
29	23	286	8.0	11	47.8	7	30.4	5	21.7
30	25	361	6.9	10	40.0	5	20.0	10	40.0
31	43	538	8.0	18	42.0	14	32.5	11	25.6
32	46	720	6.4	34	73.9	7	15.0	5	11.1
33	65	887	7.3	38	58.5	15	23.1	12	18.5
34	82	1,062	7.7	52	63.4	19	23.2	11	13.4
35	86	1,234	7.0	55	63.9	19	22.1	12	14.0
36	72	1,349	5.3	39	54.2	17	25.0	16	22.2
37	55	1,318	4.2	36	65.4	12	21.8	7	12.7
38	82	1,724	4.7	49	59.7	15	18.3	18	22.0
39	74	1,666	4.4	45	60.8	12	16.2	17	23.0
40	99	1,919	5.1	78	77.7	9	9.1	12	12.1
41 (6 mo.)	65	920	7.1	50	77.0	8	12.3	7	10.7
Totals	861	14,594	5.9	543	63.1	165	19.2	153	17.7

Birth Weight.—The stillbirth and neonatal mortality data by birth weights, in increments of 250 Gm., are presented in Table II. As anticipated, there were few survivors in the group weighing under 1,250 Gm. (2 pounds and 12 ounces), but the fatality rate decreased rapidly as the birth weight increased.

TABLE II. STILLBIRTH AND INFANT MORTALITY IN RELATION TO BIRTH WEIGHT

GRAM WEIGHT GROUP	NO. OF CASES	GROSS MORTALITY		STILLBIRTHS NO. OF CASES	DIED UNDER ONE MONTH NO. OF CASES	DISCHARGED ALIVE NO. OF CASES
		NO. OF CASES	PER CENT			
700- 999	39	39	100	23	16	0
1,000-1,249	37	33	89.2	22	11	3
1,250-1,499	66	51	76.7	22	29	16
1,500-1,749	78	47	60.2	16	31	32
1,750-1,999	125	56	44.8	28	28	70
2,000-2,249	199	43	21.6	24	19	154
2,250-2,499	315	48	15.2	29	19	269
No data	2	1	50.0	1	0	1
Totals	861	318	36.9	165	153	543

Syphilis.—Thirteen (31.1 per cent) of the 41 infants born to women with positive serologic reactions were syphilitic, and 9 of the 13 died before discharge, an immediate mortality rate of 61.5 per cent.

Complications of Pregnancy and Labor.—The effect of various complications of pregnancy and labor occurring among 263 patients is presented in Table III. In each category the fetal salvage was less than in the uncomplicated cases. Among the 224 patients with nonconvulsive toxemia, labor was induced in only 84. Seven out of 11 women with eclampsia were not induced, whereas all those with placenta previa were started in labor by the procedures utilized to control the bleeding.

TABLE III. INFANT MORTALITY IN RELATION TO THE COMPLICATIONS OF PREGNANCY AND/OR LABOR

COMPLICATIONS	TOTAL NO. OF CASES	FETAL SALVAGE		STILLBIRTHS		INFANT DEATHS UNDER ONE MONTH	
		NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Toxemia, nonconvulsive	224	120	53.6	69	30.8	35	15.6
Eclampsia	11	4	36.4	6	54.5	1	9.1
Placenta previa	27	7	25.9	14	51.8	6	22.3
Prolapsed cord	12	1	8.3	11	91.7	0	0.0
Premature separation of the placenta	10	0	0.0	9	90.0	1	10.0
Diabetes mellitus	4	1	25.0	3	75.0	0	0.0
Intra-partum infection	9	4	44.4	5	55.6	0	0.0
No complications	598	415	69.3	72	12.1	111	18.4

Intra-partum fever followed the induction of labor by Voorhees bag (2) and by premature rupture of the membranes (4), and also occurred after spontaneous onset (3).

TABLE IV. RELATION OF METHOD OF DELIVERY TO FETAL MORTALITY

METHOD OF DELIVERY	TOTAL CASES	MORTALITY	
		NO. OF CASES	PER CENT
Spontaneous	631	213	33.8
Breech	79	29	36.7
Low forceps	56	17	30.4
Version and extraction	38	24	63.2
Cesarean section	21	11	52.4
Therapeutic abortion	12	12	100.0
Midforceps	4	1	25.0
No data	20	11	55.0
Totals	861	318	36.9

One hundred and twenty-three out of 142 previable babies (under 1,500 Gm.) died in comparison to 195 among 619 prematures (1,500 to 2,499 Gm.).

Type of Delivery.—The relation between the method of delivery and the fetal and infant mortality rates is shown in Table IV. The high death rates after version and extraction and therapeutic abortion may be explained by the relatively high incidence of children weighing under 1,500 Gm. In the entire series there were 142 previable infants with only 19 (13.4 per cent) survivors. In forceps deliveries and in breech extractions, the babies were generally larger and thus withstood the trauma of birth more satisfactorily.

The fact that there were 20 cesarean sections (21 infants) with such a high fetal and infant death rate deserves some attention. All of these operations were performed prior to July, 1938, and except in one instance, sterilization was carried out at the same time. There were 12 cases (two patients had a coincidental toxemia) where previous cesarean section was the primary indication for the procedure and where the time of operation was set by the premature onset of uterine contractions. The other 8 cases included 2 patients with chronic cardiac disease, 3 with severe hypertensive vascular disease, and one each with carcinoma of the cervix, dystocia following uterine interposition, and pre-eclampsia

with marked vulval edema, precluding vaginal delivery. These 8 mothers delivered 9 infants, of whom 3 survived (37.5 per cent), while only 6 of the 12 babies born to mothers who were subjected to operation because of previous cesarean section were discharged alive. Five of the children weighed less than 2,000 Gm. and only 2 survived; while among the 12 who weighed between 2,000 and 2,499 Gm., there were 3 stillborn and macerated, 2 that died within three days, and 7 survivors. Such data emphasize again the fact that abdominal delivery is not a child-saving operation, even when there are no maternal complications.

Duration of Labor.—The total duration of labor was available for 760 cases. The fetal and infant mortality was greatest (45.3 per cent, or 44 deaths in 97 cases) when parturition lasted less than three hours, and least (29.7 per cent, or 14 deaths in 48 cases) when labor was prolonged more than thirty hours. The two factors which evidently explain this apparently anomalous situation are that rapid labors (1) occurred more commonly with smaller fetuses, and (2) were associated with more extensive fetal damage due to the rapid molding of the head and to the generally greater force of the uterine contractions.

Sedation and Anesthesia.—There was no correlation between the type of sedation and the infant survival rate, except in the case of morphine, which was given to 303 mothers. The higher death rate (34.6 per cent) when this drug was exhibited alone or in combination with scopolamine or a barbiturate can be explained by its employment in large doses (gr. ½ to 3) in patients with severe toxemia. When ordinary sedative doses were given, there was no significant difference in the rates of fetal survival. Some degree of asphyxia was noted in 84 (16.9 per cent) of the 499 cases where no sedative was given, as against 105 (34.6 per cent) of the 362 instances where morphine or some other sedative drug was administered. Among the 208 autopsied infants, there were 21 who showed pneumonia as the probable cause of death; in 16 instances (72.7 per cent) no analgesia had been given the mother.

Some form of anesthesia was given to 733 mothers as follows: ethylene, 477; ethylene and ether, 46; ether, 35; chloroform, 72; cyclopropane, 43; nitrous oxide, 21; nitrous oxide and ether, 5; pudendal block, 15; various others, 19. Among the 82 severely asphyxiated infants, there were 13 cases where no anesthetic had been used, an incidence of 10.0 per cent. By contrast, 45 severely asphyxiated children were born to mothers who received ethylene alone, 9.4 per cent. This would make it seem that the type of anesthetic agent employed played a relatively small role in the production of severe asphyxia.

Induction of Labor.—The induction of labor was carried out 251 times, with complete data available for 223 cases; among which there were 125 elective and 98 indicated inductions. The 125 elective inductions represent approximately 0.3 per cent of those carried out over the fifteen-year period, and were regarded as errors in judging the size of the unborn child. By refusing to resort to elective induction until the patient has reached the calculated date of confinement, such mistakes can be materially reduced. There were six twin pregnancies among the 125 in the elective series, and a total mortality of 26 (19.1 per cent) including 11 stillbirths, among the 131 infants. In contrast, the fetal and infant mortality in the indicated inductions was 52.9 per cent, undoubtedly greater because of the higher incidence of more immature infants.

Causes of Fetal and Infant Deaths.—Among the 318 children, who were stillborn or died during the first month of life, 208 (65.4 per cent) were subjected to post-mortem study, and 218 anatomic diagnoses were given as possible causes of death:

Prematurity (no other findings)	4
Atelectasis	73
Intracranial hemorrhage	44
Congenital anomaly	27
Pneumonia	21
Miscellaneous infections	9
Subscapular hemorrhage	6
Hemoperitoneum	2
Asphyxia (prolapsed cord)	2
Undetermined	30
Total	218

In four instances no diagnosis other than prematurity could be made, but in the remaining cases there were associated demonstrable pathologic lesions. The high incidences of atelectasis (35.1 per cent) and intracranial hemorrhage (21.2 per cent) were to have been anticipated, since prematurity is known to increase the susceptibility to such conditions. On the other hand, anomalies were probably responsible per se for early delivery. Hemoperitoneum may be blamed on too strenuous efforts at resuscitation by younger staff officers and students who did not recognize the need for gentleness. Subscapular hemorrhage was probably due to the trauma of delivery and deaths from this cause may be attributed to shock. Fifteen of the 21 infants dying from pneumonia were stillborn (1), or died within forty-eight hours (14), and may be presumed to have contracted the infection in utero.

The clinical causes of death in the 110 infants not subjected to post-mortem examination included:

Prematurity	38
Maternal toxemia	20
Intracranial hemorrhage	15
Placenta previa	13
Syphilis	5
Intercurrent infection (mother)	3
Abruptio placentae	4
Prolapsed cord	2
Undetermined	10
Total	110

When "prematurity" alone was diagnosed, there was no reasonable clinical explanation for the early termination of the pregnancy. The parity of the mother did not influence the clinical causes of death among the premature infants, except that placenta previa was more common (12 to 1) among multigravidas in the series, whereas syphilis appeared more frequently in the primigravidas.

COMMENT

Any newborn infant weighing less than 2,500 Gm. has an increased chance of being stillborn or of dying during the first year of life. In approximately one-third of the cases, some complication of gestation,

such as toxemia, multiple pregnancy, ante-partum bleeding, or intercurrent maternal disease, either leads directly to the early termination of the pregnancy or supplies the medical indication for interruption. In the remainder, the premature birth seems to be brought about by biologic factors of which our knowledge is scant and against which we can offer little protection. In the former group, prenatal care appears to offer very little except in maternal syphilis and in certain cases of toxemia, where there is practically no chronic damage to the vascular or renal apparatus, while in the latter its effects are problematic unless conditions are such that the probable hazards of faulty nutrition, overwork, and endocrine unbalance can be attacked successfully. The chief hope of improving the mortality rate from prematurity at present seems to lie in giving more adequate care to the child that is born before it is fully equipped for extrauterine life. This includes not only postnatal care, but attention to various parturitional factors, which appear to have a potent effect upon the child's chances.

In general, the fate of a prematurely born child depends more upon its actual weight at birth than upon any other factor. This fact forms the basis for the common practice of delaying artificial termination of a pregnancy as long as possible in the face of a disease complication which is best treated by emptying the uterus, as, for example, the toxemias of late pregnancy. It is, however, common knowledge that such a course frequently leads to intrauterine fetal death and thus defeats its own objective. Choice of the proper time for intervention in such cases demands fine judgment for which no acceptable criteria are available.

Syphilis is one disease, the detection and treatment of which during early pregnancy constitues a distinct triumph for antenatal care. The present tendency toward laws making serologic tests for syphilis compulsory in pregnant women should eventually almost eliminate this disease as a cause of prematurity.

Available data emphasize the importance of the conduct of premature labor in the interests of the child. Rapid delivery, especially that completed within less than three hours, is associated with a high mortality rate, since the premature infant is unable to withstand the forceful uterine contractions incidental to such quick expulsion. Spontaneous delivery with adequate episiotomy is probably the safest, although carefully performed forceps extraction entails little or no additional risk. Delivery of the aftercoming head (breech extraction or podalic version) carries a high risk of fatal injury, largely because of the necessity for rapid cranial molding or of asphyxia due to delay in extracting the relatively large head. Abdominal delivery even in the presence of no serious maternal complications involves such an unexplained mortality as to remove it from the child-saving category.

Sedation by the administration of ordinary sedative doses appears not to increase the fetal risk, but larger doses, especially of morphine, with or without other analgesics, double the incidence of asphyxia and add appreciably to the fetal death rate. The type of inhalation anesthetic agent appears not to alter the fetal prognosis significantly, although undoubtedly the depth of anesthesia is a factor; local anesthesia would seem to be preferable.

Induction of labor in itself appears not to prejudice the child, although the condition for which the induction is carried out may alter the outcome unfavorably. Elective induction should obviously be restricted to infants, who are mature both on the basis of menstrual age and of clinical estimation.

Pulmonary atelectasis, intracranial hemorrhage, developmental anomalies, and pneumonia, are, in order, the most frequent causes of fetal or infant death, while toxemia and ante-partum bleeding are the most common clinical causes. Little can be done prophylactically in any of these conditions, except in the case of intracranial hemorrhage, which may possibly be prevented by the administration of vitamin K to the mother before or during labor. The fact that such a large percentage of pneumonia is apparently contracted in utero makes it difficult to combat the infection successfully.

Adequate postnatal care of the prematurely born child still involves the traditional triad of nursery responsibilities: the provision of satisfactory nourishment, the maintenance of proper temperature, and the avoidance of infection, which last is at least partly implemented by the maintenance of high relative humidity.

SUMMARY AND CONCLUSIONS

Among 861 consecutive prematurely born children, weighing from 700 to 2,499 Gm., there were 318 (36.9 per cent) who were stillborn or died before the end of the first month, and an additional 36 (4.2 per cent) who died before the end of the first year.

The series included 142 "previable" children weighing less than 1,500 Gm., of whom only 19 (13.4 per cent) survived. Excluding this entire group leaves 719 children with 524 survivors (72.9 per cent) to the end of the first month.

Analysis reveals that there is little possibility, with our present inadequate knowledge, of preventing any significant number of premature births, and that the burden for decreasing the death rate among these infants lies chiefly with improved natal and postnatal care.

The avoidance of other than mild maternal sedation and the use of local anesthesia, together with delivery by spontaneous expulsion or careful forceps extraction following episiotomy appear to offer the best prognosis. The induction of labor, unless indicated by definite medical

conditions, and attempts to hasten delivery by augmenting the strength of uterine contractions are inadvisable. Abdominal delivery does not give satisfactory fetal salvage and is not to be viewed as a child-saving procedure.

Proper postnatal care involves gentle and adequate resuscitatory measures, small frequent feedings, preferably of breast milk, according to a definite schedule, such as that advanced by Marriott and Jeans (1941), careful regulation of the environment in a modern incubator or premature room with attention not only to the temperature but also to the relative humidity of the air.

When the relative humidity of the nursery was maintained at approximately 50 per cent, and all individuals with upper respiratory infections were excluded, masking and gowning did not materially affect the survival of prematurely born infants.

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THE ESTROGENIC PROPERTIES OF DIHYDROSTILBESTROL (HEXESTROL)

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THE new synthetic estrogenic drug diethylstilbestrol is satisfactorily replacing the use of natural estrogens. Since stilbestrol occasionally produces nausea, the authors have searched for an alternative drug which might be equally satisfactory in therapeutic results without this side effect. Bishop and his coworkers[1] reported upon the estrogenic properties of stilbestrol dipropionate and dihydrostilbestrol, called by them hexestrol.* A similar study of diethylstilbestrol previously reported by the authors[2] has been used for comparison.

The name hexestrol has been used rather than the more descriptive one of dihydrostilbestrol to prevent confusion with diethylstilbestrol. Bishop and his associates found this drug less toxic than stilbestrol and also less potent in estrogenic properties. The dose employed by them was much smaller than that found necessary to give satisfactory results in this study. Details of the structure and synthesis of hexestrol may be found in the above-mentioned article. The following report is concerned chiefly with two factors: so-called toxicity as manifested by nausea, and estrogenic potency as evidenced by clinical results. All

*Supplied by Eli Lilly and Co. for investigational purposes.

patients were given the uncoated tablets administered orally before meals, with the exception of certain cases of senile vaginitis in which the tablets were used as vaginal suppositories.

TABLE I. THE INCIDENCE OF NAUSEA PRODUCED BY HEXESTROL

DAILY DOSE	NO. PATIENTS TREATED	NO. EXHIBITING NAUSEA
Less than 5 mg.	28	0
5 mg.	12	0
10 mg.	19	5
15 mg.	13	0
20 mg.	7	1
40 mg.	1	1
Total	80	7 or 8.75%

As can be seen from Table I, the incidence of nausea for all cases is 8.75 per cent. In a previous report of 115 patients treated with stilbestrol under similar conditions, the incidence of nausea was reported as 6.3 per cent, and in those patients receiving 1.0 mg. per day or less, the incidence was 4.1 per cent. Table I clearly indicates that hexestrol will produce nausea, particularly in large doses. Of the 7 patients exhibiting nausea, in only two was it sufficiently severe to be disturbing. These two, evidencing nausea upon 20 and 40 mg. daily, respectively, promptly were relieved when the dose was reduced by one-half. The other 5, all receiving 10 mg. daily, readily established tolerance without reduction of the daily dose in from three to six days.

All 7 patients manifesting nausea with hexestrol were later placed upon 1.0 mg. of diethylstilbestrol daily, and two again developed nausea but 5 did not. Conversely, two patients who have repeatedly become severely nauseated with the administration of 1.0 mg. of stilbestrol daily were changed to 10 mg. of hexestrol daily with complete disappearance of untoward effects and continued relief of symptoms.

Clinical evaluation of the estrogenic activity of hexestrol has been made by a study of its effects upon the menopause, dysmenorrhea, lactation, senile vaginitis and vulvovaginitis in children. Several cases of functional bleeding were treated, but as they are of no value to this report and the results are inconclusive they have not been included.

Thirty-seven menopausal patients, 17 natural and 20 artificial, were given hexestrol. None had previously responded to sedatives alone. Twenty-four responded excellently to the drug, 3 fairly well, and 10 poorly or not at all. A study of 18 of these patients all of whom had at some time previously been treated with natural estrogens or stilbestrol is presented in Table II. Fourteen had recurrence of symptoms after a rest interval of at least four months before hexestrol was begun. Four responded poorly or not at all to stilbestrol and were changed to hexestrol without a rest interval.

The significant feature is that 3 patients who failed to respond to an adequate course of stilbestrol, 1.0 mg. daily for twenty-eight days, reported prompt relief of symptoms when placed on hexestrol. On the other hand, some who responded well to stilbestrol responded poorly or not at all to hexestrol. It is the authors' experience that the dose of hexestrol which will roughly correspond to 1.0 mg. of stilbestrol is 10 mg.

TABLE II. COMPARISON OF EFFECTS OF STILBESTROL AND DIHYDROSTILBESTROL

STILBESTROL DAILY MG. DOSE	RESPONSE	HEXESTROL DAILY MG. DOSE	RESPONSE
1.0	Excellent	1.0	None
1.0	Poor	1.0	Excellent
1.0	Excellent	3.0	Excellent
1.0	Excellent	4.0	Fair
1.0	Excellent	4.0	Fair
1.0	Excellent	4.0	None
1.0	Excellent	5.0	None
1.0	Poor	5.0	Fair
1.0	Excellent	6.0	None
1.0	Excellent	10.0	Excellent
1.0	Excellent	10.0	Excellent
1.0	Excellent	10.0	Excellent
1.0	None	10.0	Excellent
1.0	None	15.0	Excellent
1.0	Excellent	15.0	None
1.0	Excellent	20.0	Excellent
Natural Estrogen Total Dose			
120,000 I.U.	Excellent	2.0	Excellent
120,000 I.U.	Excellent	4.0	Excellent

Eight patients with primary dysmenorrhea were treated with hexestrol. Three were also given stilbestrol for purposes of comparison. The regular practice in the endocrine clinic of the department of gynecology is to administer a daily dose for fourteen successive days, beginning with the first day of menstruation. The effect is then noted upon the following period. The results are reported in Table III. The first 4 patients were treated for two successive cycles with the drugs in the order listed.

TABLE III. RESULTS IN TREATMENT OF DYSMENORRHEA

CASE	DRUG USED	DAILY DOSE	RESPONSE
1	Hexestrol	3.0 mg.	Fair
	Stilbestrol	1.0 mg.	Excellent
2	Hexestrol	2.0 mg.	None
	Stilbestrol	1.0 mg.	Excellent
3	Hexestrol	5.0 mg.	None
	Stilbestrol	1.0 mg.	None
4	Hexestrol	1.0 mg.	None
	Hexestrol	5.0 mg.	Excellent
5	Hexestrol	10.0 mg.	Excellent
6	Hexestrol	10.0 mg.	Excellent
7	Hexestrol	15.0 mg.	Excellent
8	Hexestrol	15.0 mg.	Excellent

Hexestrol was administered to two patients for the suppression of lactation. These are reported as such.

CASE 1.—A 17-year-old colored female, six months post partum, was lactating freely from both breasts although she had stopped nursing her child two weeks prior. She had had no menses since previous to the onset of her pregnancy. Twenty milligrams of hexestrol were administered daily for seven days at the end of which time lactation ceased in both breasts. Three days after the drug was discontinued the patient menstruated for two days.

CASE 2.—A 26-year-old colored female was operated upon for an unruptured tubal pregnancy. On the fifth postoperative day the patient developed engorged and painful breasts and began to lactate profusely. She was given 40 mg. of hexestrol daily for three days and experienced considerable relief of the engorgement. She also developed severe nausea and vomiting. The dose was then reduced to 20 mg. daily and at the end of four more days lactation had ceased and the nausea and vomiting had cleared up. Bromsulfthalein and hippuric acid liver function tests were normal at the end of treatment. The patient received a total of 200 mg. in seven days. There was no withdrawal bleeding.

Four patients complaining of senile vaginitis were treated with oral hexestrol. Three received 10 mg. daily for from one to three weeks without response. One received 20 mg. daily for one week with excellent response. The three who had experienced no relief and one other patient who was not given oral therapy were instructed to use a 5 mg. tablet as a vaginal suppository morning and night. In all 4, an atrophic, ulcerated vaginal mucosa was converted to a thick, more normal, one with relief of symptoms at the end of a week of treatment. The local response was not as marked as that usually observed under the influence of amniotin perles of 1,000 I.U. each, and in contrast the thickened mucosa produced by hexestrol was observed to be rather dry and furry in appearance without much desquamation.

Twelve children with gonococcal vulvovaginitis received oral hexestrol. The results are presented in Table IV. Two of these patients developed slight bilateral breast hypertrophy on 1.0 and 2.0 mg. daily for seven days, respectively. This subsided in both within four weeks after the drug was discontinued. This small series of children compares more than favorably with a similar series treated with oral diethylstilbestrol in identical dose and previously reported by the authors.[3] It is even suggested that hexestrol may have a more selective action upon the prepubertal vaginal mucosa than does stilbestrol.

TABLE IV. RESULTS OF VULVOVAGINITIS TREATED WITH HEXESTROL ORALLY

AGE	DAILY MG. DOSE	TOTAL MG. DOSE	RESULTS IN TERMS OF VAGINAL SMEAR AND pH
2	1.0	7.0	Negative smear, pure adult epithelium and pH of 4.5
5	1.0	7.0	Negative smear, pure adult epithelium and pH of 4.5
2	1.0	7.0	Negative smear, pure adult epithelium and pH of 6.0
2	1.0	7.0	Negative smear, pure adult epithelium and pH of 4.5
2	1.0	14.0	Negative smear, pure adult epithelium and pH of 4.5
1½	1.0	14.0	Negative smear, pure adult epithelium and pH of 4.5
2	1.0	14.0	Negative smear, pure adult epithelium and pH of 4.5
8	2.0	14.0	Negative smear, pure adult epithelium and pH of 4.5
8	2.0	14.0	Negative smear, pure adult epithelium and pH of 4.5
6	2.0	14.0	Negative smear, pure adult epithelium and pH of 4.5
5	2.0	20.0	Negative smear, pure adult epithelium and pH of 4.5
7	2.0	28.0	Negative smear, pure adult epithelium and pH of 4.5

A few patients exhibited other untoward effects aside from nausea. Exclusive of the patients with an artificial menopause and with functional uterine bleeding of 43 patients who were given oral hexestrol withdrawal bleeding was noted in 4, or 9.3 per cent. None of these exhibited any bleeding during the administration of the drug. This compares well with a similar series of 99 patients treated with diethylstilbestrol in whom the incidence of bleeding was 13.9 per cent. Breast discomfort was noted in two of the 37 menopausal patients during

treatment. This discomfort quickly disappeared when the drug was discontinued. No other untoward effects of the drug were noticed.

CONCLUSIONS

Hexestrol is a potent synthetic estrogenic drug. It may be satisfactorily substituted for diethylstilbestrol in an attempt to overcome nausea or to produce a better clinical response in a patient resistant to the latter drug. When used in sufficient dose it may produce nausea. This is milder than that produced by comparable doses of stilbestrol and responds quickly to reduction of the amount administered. The effective dose in adults has been found to be about ten times that of diethylstilbestrol. In children, oral hexestrol is, if anything, more effective than oral stilbestrol in equal dose when used to treat vulvovaginitis. The authors recommend that this drug be given extensive trial as an alternative drug to diethylstilbestrol.

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Yerushalmy, Gardiner and Palmer: Studies in Childbirth Mortality. III. Puerperal Fatality in Relation to Mother's Previous Infant Losses, Pub. Health Rep. **56**: 1463, 1941.

This paper deals with puerperal fatality and late fetal and neonatal mortality in their relation to the mother's previous infant losses. Among others, the following findings are recorded:

Of the 161,177 births of orders two and over entering into this study, 76.9 per cent were to mothers whose previous issue had all survived and 23.1 per cent were to mothers who had lost one or more previous children.

The rates of loss of both mother and infant were about twice as high in the group with a history of previous loss as in the group with no previous loss.

The higher the number of previous losses to the mother, the greater was the chance of death to both mother and infant. The increase with advancing number of previous losses was more pronounced for the loss of offspring than it was for the loss of mother.

The higher rates for puerperal fatality and for infant loss associated with previous losses were present to a considerable degree in the premature as well as in the full-term deliveries. The puerperal fatality rate for full-term deliveries was 16.0 among mothers with no history of previous losses and 25.8 among mothers who had lost one or more of their previous children. The corresponding rates among the premature deliveries were 134.1 and 179.4, respectively. Similarly, the late fetal and neonatal mortality rates were 20.0 and 47.1 among full-term births and 501.4 and 670.0 among the premature.

The suggestion is made that the father also may play an important part in these cases of repeated losses in the family.

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VAGINAL TRICHOMONIASIS*

Complement Fixation, Puerperal Morbidity, and Early Infection of Newborn Infants

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COMPLEMENT FIXATION

LITTLE is known of the serologic phenomena which develop in response to vaginal trichomonads. Wendlberger,[10] using an alcoholic extract of an impure culture of the protozoa as antigen, demonstrated complement fixing reactions in 22 of 32 infected women. Sixteen uninfected women gave negative reactions, as did carriers with no manifestations of vaginal disease. The 22 women who gave reactions had abnormal discharges, with or without vaginitis.

Four hundred consecutive obstetric patients admitted to the University Hospital were studied ante and post partum by "hanging drop" and culture techniques for *Trichomonas vaginalis* as a necessary preliminary to the evaluation of the complement fixation tests.

For the examination of fresh specimens discharge from the lower vagina and from the posterior fornix was collected on sterile cotton applicators which were agitated in small tubes containing 1 c.c. of Ringer's solution. The suspensions were spread on glass slides and examined promptly for motile trichomonads under the low-power lens system. Cultures were made by placing similar applicators coated with discharge from the same areas into tubes of 5 per cent human serum in Locke's solution over placenta infusion agar.[11] The sediment in the bottom of the tubes was examined within twenty-four hours for motile protozoa.

Material was obtained from the lower vagina and posterior fornix before delivery and from the lower vagina post partum. The results, as tabulated in Table I, indicate a slight superiority of examination of fresh vaginal discharge over the culture technique. On the other hand a few specimens revealed trichomonads only in culture.

It is believed that examination of fresh vaginal discharge is adequate for routine diagnosis. Cultures are employed routinely in this clinic but their chief value lies in demonstrating the organisms in an occasional patient under treatment in whom examination of the fresh discharge is negative. The disadvantages lie in the preparation of the media, which is simple but time consuming, and in the fact that twenty-four hours must elapse before the results can be obtained.

*This report is an extension of a study of *Trichomonas vaginalis* Donné which has been in progress for several years.[1-9]

TABLE I. COMPARISON OF "HANGING DROP" AND CULTURE TECHNIQUES FOR THE DIAGNOSIS OF TRICHOMONAS VAGINALIS*

	76 PATIENTS POSITIVE BOTH ANTE AND POST PARTUM					18 PATIENTS POSITIVE ONLY ANTE PARTUM				16 PATIENTS POSITIVE ONLY POST PARTUM			
	HD+ C+	HD- C+	HD+ C-	HD- C-	No Culture	HD+ C+	HD- C+	HD+ C-	HD- C-	HD+ C+	HD- C+	HD+ C-	HD- C-
Vagina	55	2	16	3	-	11	1	6	-	-	-	-	16
Post. Fornix	55	3	12	6	-	12	1	2	3	-	-	-	16
Post partum	59	4	7	-	6	-	-	-	18	14	2	-	-

*HD, Hanging drop; C, culture.

Ante-partum venous blood specimens were tested for the presence of complement-fixing antibodies by the technique of Kolmer.[12] A bacteria-free suspension of *Trichomonas vaginalis*[1, 2] in physiologic saline solution was used as antigen. These organisms were grown in a simple peptone human-serum carbohydrate medium and were repeatedly washed before use, thus insuring an antigen in which the only complex elements foreign to the human body were the components of the trichomonads.

The results are presented in Table II. Patients infected with *Trichomonas vaginalis* were three times as likely to have positive serologic reactions as were uninfected women.

TABLE II. COMPLEMENT FIXATION DATA

FOUR HUNDRED ANTE-PARTUM OBSTETRIC PATIENTS			
	NUMBER	POSITIVE COMPLEMENT FIXATION	
		NUMBER	PER CENT
Trichomonas positive	110	52	47.27
Trichomonas negative	290	48	16.55

Reclassification of 399 of these patients on the basis of objective vaginal changes present at sterile ante-partum speculum examination gives the results shown in Table III. These data indicate that patients with abnormal discharge and/or vaginal inflammation are more likely to give positive complement fixation reactions, but that there was a considerable percentage of reactors among patients with no objective pathologic changes in the vagina. This contradicts the findings of Wendlberger but is more in line with what might be expected from an immunologic point of view. There are many infectious diseases such

TABLE III

TRICHOMONAS	NO.	ABNORMAL DISCHARGE				ABNORMAL DISCHARGE AND/OR INFLAMMATION				NORMAL DISCHARGE AND MUCOSA			
		NO.	%	C. F.*	%	NO.	%	C. F.*	%	NO.	%	C. F.*	%
Positive Present	109	65	59.6	32	49.1	28	25.6	13	46.4	16	14.6	6	37.5
Negative Absent	290	184	63.4	37	20.1	23	7.9	3	13.0	83	28.6	8	9.6

*C.F., Positive complement fixation.

as typhoid fever from which a patient may completely recover and be free from the offending organisms but still give positive serologic reactions. There is no evidence to oppose a similar possibility for vaginal trichomoniasis. Such a hypothesis would explain positive reactions in women in whom no trichomonads could be demonstrated; they may have been infected but have undergone spontaneous cure. Cross reactions with oral and intestinal trichomonads have not been excluded.

No practical importance is attached to the demonstration of complement fixing reactions at this time. Certainly the test is of no diagnostic value, and it remains to be seen whether there is any correlation with spontaneous or therapeutic cure.

PUERPERAL MORBIDITY

It has long been the contention of certain investigators that *Trichomonas vaginalis* in the pregnant woman is a source of danger during the puerperium and many advocate treatment of the infection during pregnancy as a prophylactic measure. If trichomonads are a provocative factor in puerperal febrile morbidity a study of the puerperal records of a large series of women in whom the presence or absence of trichomonads has been established should offer evidence of such action. With this in mind the post-partum temperature data on 880 women delivered in this clinic have been reviewed and the results listed in Table IV.

TABLE IV. PUERPERAL FEBRILE MORBIDITY; 880 OBSTETRIC PATIENTS

	ONE DAY FEVER	MORBID PUERPERIUM	TOTAL PATIENTS
Patients with *T. vaginalis*	32, or 14.3%	19, or 8.5%	223
Patients without *T. vaginalis*	87, or 11.7%	55, or 8.3%	657

The significance of one-day fever is not understood, but it is doubtful whether its slightly higher incidence in association with the presence of *T. vaginalis* could be attributed to the abnormal bacterial flora usually present with this vaginal infection. It is obvious that women with *T. vaginalis* have no increased tendency to prolonged fever during the puerperium.*

These data support the idea that vaginal trichomoniasis in pregnancy should not necessarily be treated, unless associated vulvovaginitis produces discomfort.

NATURAL TRANSMISSION TO BABIES

There are undoubtedly multiple modes of transmission of *Trichomonas vaginalis*. Cross contamination from one woman to another and sexual intercourse probably play major roles. Early childhood

*Post-partum temperatures were taken every four hours. One-day fever is defined as a temperature of 100.4° or more occurring during any single day after the first twenty-four hours. Morbid puerperium is defined as one in which the temperature reaches 100.4° or more during two or more days.

infections can usually be explained on the basis of contamination, but the possibility exists that female babies born to infected mothers may become infected during birth. With this possibility in mind, 41 such babies were examined within the first eight days of life. Hanging drop preparations were made from the vagina and introitus, usually on the fourth and eighth days, although in some instances only one examination was undertaken. Two babies (4.8 per cent) were found infected; in both the first examination was negative but the second revealed motile trichomonads, including dividing forms. Since the babies could not be followed for more than eight days, the duration of their infections is unknown. It is not illogical to assume that the trichomonads can exist for many years as a latent infection in young children as is known to be true in adult women. On the other hand, changing biologic conditions in the infant vagina, notably a shift in pH, may militate against persistence of the infection.

SUMMARY

Examination of fresh vaginal discharge is the more practical and economical way to diagnose the presence of *Trichomonas vaginalis*. Cultures are highly satisfactory but add little to the study.

Approximately 50 per cent of women infected with *T. vaginalis* gave positive complement fixation reactions, which were noted less often in carriers than in women with vaginitis. One-sixth of women in whom *Trichomonas vaginalis* could not be demonstrated also gave positive reactions. It is not improbable that some of these women had been previously infected.

Trichomonas vaginalis infection is not associated with an increase in puerperal morbidity and its presence does not constitute an indication for treatment in asymptomatic patients.

Approximately 5 per cent of female babies born to infected mothers were shown to be infected with *Trichomonas vaginalis* during the first eight days of life.

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METHODS FOR THE OBJECTIVE EVALUATION OF ESTROGEN THERAPY IN THE MENOPAUSE*

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AS ENDOCRINE therapy has become established as a reliable part of the physician's armamentarium, there has been a concomitant effort to devise objective laboratory tests whereby the therapeutic uses of endocrine preparations may be controlled accurately. In dysfunctions of the thyroid gland the basal metabolic rate has been found a dependable index of thyroid activity. In diabetes mellitus, the blood and urinary sugar levels have proved invaluable guides in regulating insulin dosage. As the principle of estrogen replacement therapy has become accepted as sound in the management of menopausal patients, the need for similarly reliable objective checks on estrogen therapy has become apparent. In the menopausal syndrome, perhaps more so than in any other endocrine disorder, there is quite often an admixture of psychologic difficulty, social maladjustment, and actual organic disease co-existing with symptoms of estrogen deficiency. The conscientious practitioner is, therefore, confronted with the often difficult problem of evaluating properly the extraendocrine factors, and of giving his patient the benefit of sufficient estrogen therapy at the same time.

Unfortunately no single laboratory test has yet been devised whereby the adequacy of estrogen replacement therapy in the menopause may be objectively evaluated with accuracy. By the utilization of certain physiologic facts, however, it is easily possible to demonstrate the existence of estrogen deficiency and to estimate roughly the extent of estrogen activity resulting from estrogen therapy. For these purposes several methods of checking have been developed including observation of histologic changes in vaginal smears and biopsies, observation of histologic changes in endometrial biopsies, and determination of the levels of estrogenic substance and follicle-stimulating hormone in the blood and urine.

These methods have been used by various investigators in establishing the relationship between estrogen deficiency and the typical vasomotor symptoms of the menopausal syndrome, in proving the potency of natural and synthetic estrogen preparations, and in determining the relative efficiency of various routes and forms of estrogen administration. In this way they have been of value.

*This study was made possible by a grant from The Rockefeller Foundation Fluid Research Fund.

Furthermore it would seem that one or the other of these laboratory procedures might be useful to the clinician as an aid in selecting those menopausal patients most likely to benefit from estrogen therapy and in guiding him in regulating the estrogen regime for the individual patient. It is for the purpose of evaluating these tests in terms of clinical usefulness that this study has been undertaken.

URINARY CONTENT OF ESTROGENIC SUBSTANCES

Failure of ovarian function is now almost universally accepted as the primary cause of the menopause. This ovarian failure with marked impairment, if not total loss, of estrogen supply has formed the basis for the rationale of estrogen replacement therapy. Since this is the case, it might logically be expected that patients with menopausal symptoms would have an absence or very low level of estrogenic substance in the urine, and that an increase of the estrogen to normal levels would go hand-in-hand with a disappearance of menopausal symptoms.

TABLE I. RESULTS OF 324 URINARY ESTROGEN ASSAYS IN 80 MENOPAUSAL WOMEN

	NO. OF SPECIMENS	0 TO 3 R.U. /24 HOURS	3 TO 10 R.U. /24 HOURS	OVER 10 R.U. /24 HOURS
Untreated Menopausal Patients				
Patients with symptoms	79	70.9%	22.8%	7.3%
Patients without symptoms	17	64.7%	35.3%	0
Estrogen-Treated Menopausal Patients				
Patients with symptoms	76	9.2%	77.6%	13.2%
Patients without symptoms	152	3.3%	75.7%	21.0%

In Table I are summarized the results of 324 urinary estrogen assays on 80 menopausal patients with and without symptoms, before and during therapy with estrogenic substances. By way of explanation, it should be said that 0 to 3 R.U./twenty-four hours represents in our laboratory practically no detectable estrogenic substance; 3 to 10 R.U./twenty-four hours represents the lower range and 10 to 20 R.U./twenty-four hours the upper range for normally menstruating women.

It is surprising to find that the assay values in our untreated menopausal women fall into similar percentage groups whether or not the patients are having menopausal symptoms and, in those patients who have received estrogen therapy, the same general percentage distribution obtains for the symptomatic and asymptomatic alike. So, while most of the untreated patients show a definite estrogen deficiency and while most of the estrogen-treated patients show quantities of urinary estrogen comparable to those found in normally menstruating women, there apparently is no correlation between the amount of estrogen in the urine and the presence or absence of menopausal symptoms.

In order to find out if urinary estrogen levels might be of value in predicting which symptomatic patients would most likely benefit from

estrogen therapy, we have resummarized our data in Table II. Here it is seen that the percentage of patients in whom the results of estrogen therapy are unsatisfactory varies directly with the urinary estrogen level present before treatment. Those who excreted normal amounts of urinary estrogen before treatment were less likely to be relieved of their symptoms than those who excreted none or only small amounts.

We have used the same assay method as formerly.[9]

TABLE II. RELATIONSHIP BETWEEN PRETREATMENT LEVEL OF URINARY ESTROGEN IN 64 MENOPAUSAL PATIENTS WITH SYMPTOMS AND THE RESULTS OF SUBSEQUENT ESTROGEN THERAPY

PRETREATMENT URINARY ESTROGEN LEVEL	NO. OF PATIENTS	RESULTS OF SUBSEQUENT ESTROGEN THERAPY		
		SATISFACTORY	PARTIALLY SATISFACTORY	UNSATISFACTORY
0 to 3 R.U./24 hr.	46	71.7%	23.9%	5.4%
3 to 10 R.U./24 hr.	14	57.1%	28.6%	14.3%
Over 10 R.U./24 hr.	4	0	50.0%	50.0%

URINARY CONTENT OF FOLLICLE-STIMULATING HORMONE

Failure of ovarian function at the menopause is associated with or followed by an increase in the blood and urinary content of gonadotropic hormone secreted by the anterior lobe of the hypophysis. There has been rather general agreement that a demonstrable excess of gonadotropic hormone is usually present in menopausal patients,[1-9] and some have felt that a correlation between this excess and the typical vasomotor symptoms exists.[3-7] Others disagree.[8] To add to the confusion, some investigators report that the gonadotropic hormone diminishes or disappears during adequate estrogen therapy[3-5, 9] while others find no such change[7, 8] even with estrogen dosage sufficient to relieve the subjective symptoms.

TABLE III. RESULTS OF 289 URINARY GONADOTROPIC HORMONE ASSAYS IN 60 MENOPAUSAL WOMEN

	NO. OF SPECIMENS	0 R.U./LITER	25 R.U./LITER	OVER 50 R.U./LITER
Untreated Menopausal Patients				
Patients with symptoms	78	47.4%	33.3%	19.3%
Patients without symptoms	20	60.0%	35.0%	5.0%
Estrogen-Treated Menopausal Patients				
Patients with symptoms	56	46.6%	23.2%	30.2%
Patients without symptoms	135	83.7%	11.1%	5.2%

In Table III are summarized the results of 289 urinary gonadotropic hormone assays on 60 menopausal women, with and without symptoms, treated and untreated. In this table "0" indicates less than 25 R.U./liter, "25" represents more than 25 but less than 50 R.U./liter,

and "more than 50 R.U./liter" is self-explanatory. Examination of this table shows a rather general correlation between symptoms and gonadotropic excess, present in both treated and untreated groups, but more definite in the former where almost 85 per cent of assays in asymptomatic treated patients show an absence of the gonadotropic factor.

TABLE IV. RELATIONSHIP BETWEEN PRETREATMENT LEVEL OF URINARY GONADOTROPIC HORMONE IN 50 MENOPAUSAL PATIENTS WITH SYMPTOMS AND THE RESULTS OF SUBSEQUENT ESTROGEN THERAPY

PRETREATMENT URINARY GONADOTROPIC HORMONE LEVEL	NO. OF PATIENTS	RESULTS OF SUBSEQUENT ESTROGEN THERAPY		
		SATISFACTORY	PARTIALLY SATISFACTORY	UNSATISFACTORY
0 R.U./liter	26	73.1%	26.9%	0
25 R.U./liter	13	61.5%	30.7%	8.8
Over 50 R.U./liter	11	72.7%	27.3%	0

In Table IV these data are rearranged to show whether or not determination of the urinary gonadotropic hormone level before treatment would aid in predicting which patients would be likely to benefit from estrogen therapy. It is of interest to note that only one-half of the patients showed a gonadotropic excess before treatment. Analysis of the results of subsequent estrogen therapy reveals that one group fared as well as another. Therefore there seems to be no correlation between the pretreatment level of gonadotropic hormone and the subsequent success or failure of estrogen therapy.

We have used the same assay method as formerly.[9]

VAGINAL SMEARS

Papanicolaou and Shorr[10] have demonstrated that the vaginal smear in the menopausal woman typically shows atrophic changes with large numbers of leucocytes, erythrocytes, and small epithelial cells of the basal type. They were able to demonstrate that with adequate estrogen therapy the vaginal smear could be changed to the estrous type with a predominance of cornified epithelial cells, and an absence of leucocytes, erythrocytes, and the small basal epithelial cells. The opinion was set forth that these vaginal smear changes correspond rather closely with the state of subjective menopausal symptoms, and that the vaginal smear method, therefore, offers a reliable means of regulating estrogen therapy. Other investigators have subsequently utilized this procedure with varying degrees of confirmation.[11-17]

In Table V are summarized the results of 124 vaginal smears in 62 menopausal women, treated and untreated, with and without symptoms. The terms Type I, II, III, and IV represent progressive trophic changes from the completely atrophic type to the full estrous type. It will

TABLE V. RESULTS OF 124 VAGINAL SMEARS IN 62 MENOPAUSAL WOMEN

	NO. OF SPECIMENS	TYPE I	TYPE II	TYPE III	TYPE IV
Untreated Menopausal Patients					
Patients with symptoms	44	25.0%	38.6%	29.5%	7.9%
Patients without symptoms	7	0	42.9%	42.9%	14.2%
Estrogen-Treated Menopausal Patients					
Patients with symptoms	26	23.1%	11.6%	42.2%	23.1%
Patients without symptoms	47	0	8.5%	41.7%	49.8%

be seen that there is a definite tendency for patients without symptoms, whether treated or untreated, to show more evidence of estrogen stimulation than those patients who are having symptoms. However, it is equally apparent that patients may be without symptoms and still show vaginal smear evidence of estrogen deficiency, while other patients still having symptoms may show vaginal smear evidence of adequate estrogen stimulation.

TABLE VI. RELATIONSHIP BETWEEN PRETREATMENT VAGINAL SMEAR TYPE IN 25 MENOPAUSAL PATIENTS WITH SYMPTOMS AND THE RESULTS OF SUBSEQUENT ESTROGEN THERAPY

PRETREATMENT VAGINAL SMEAR TYPE	NO. OF PATIENTS	RESULTS OF SUBSEQUENT ESTROGEN THERAPY		
		SATISFACTORY	PARTIALLY SATISFACTORY	UNSATISFACTORY
Type I	4	75.0%	25.0%	0
Type II	11	63.7%	27.3%	9.0%
Type III	10	50.0%	50.0%	0
Type IV	0	------	------	----

In Table VI the pretreatment vaginal smear types in 25 cases are charted against the clinical results of subsequent estrogen therapy. Here it is seen that in general the greater the estrogen deficiency, as indicated by the vaginal smear type, the greater the likelihood that satisfactory results will be obtained with estrogens.

CERVICAL MUCUS

Utilization of still another method for estimating the adequacy of estrogen therapy in the menopause has been reported by Guttmacher and Shettles[18] who found that definite, readily demonstrable changes occur in the cervical mucus when the menopausal patient is treated with estrogens. These changes were found to simulate the cyclic changes in the character of the cervical mucus occurring regularly during menstrual life,[19-21] as regards the following factors: amount, pH, viscosity, turbidity, cellular content, penetrability by spermatozoa in vitro, and survival time of spermatozoa in contact with the mucus in vitro. In the untreated menopausal woman, the cervical mucus is quite scanty, has a pH of 4.0 to 6.0, is highly viscous or crumbly in character, is cloudy

white or yellow, contains many leucocytes and epithelial cells, is not penetrable by spermatozoa in vitro, and immobilizes spermatozoa immediately by contact. At the height of estrogen stimulation the cervical mucus becomes very abundant, flowing from the external os, has a pH of 7.5 to 8.5, is fluid-like with low viscosity, is glairy and transparent, is almost cell free, is readily penetrable by spermatozoa, and, when in contact with spermatozoa in vitro at room temperature, allows their survival for as long as twenty-four hours, even longer than their survival time in seminal plasma. Dr. L. B. Shettles has carried out complete examinations of specimens of cervical mucus from 25 of our symptomatic menopausal patients before treatment and from 41 menopausal patients who were at the time receiving estrogen therapy. The results in a portion of these cases have been included in the report of Guttmacher and Shettles.[18]

TABLE VII. CHARACTERISTICS OF THE CERVICAL MUCUS IN MENOPAUSAL PATIENTS BEFORE AND AFTER ESTROGEN THERAPY

CHARACTERISTICS OF CERVICAL MUCUS	UNTREATED MENOPAUSAL PATIENTS (25 CASES)	PATIENTS TREATED WITH 0.1 TO 0.2 MG. STILBESTROL Q.D. (10 CASES)	PATIENTS TREATED WITH 1.0 MG. OR MORE STILBESTROL Q.D. (20 CASES)	PATIENTS TREATED WITH SUBCUTANEOUS ESTROGENIC PELLETS (5 CASES)
Amount	Scanty	Moderate	Abundant	Abundant
pH	4.0-6.0	6.0-7.0	7.0-8.5	7.0-8.5
Viscosity	Tenacious	Slightly tenacious	Fluid-like	Fluid-like
Turbidity	Milky	Moderately cloudy	Transparent, glairy	Transparent, glairy
Cellular content	Many leucocytes and epith. cells	Moderate leucocytes and epith. cells	Almost cell-free	Almost cell-free
Penetrability by spermatozoa in vitro	None	Slight	Readily penetrable	Readily penetrable
Survival time of spermatozoa in vitro	None	One-half hour or less	As long as 24 hours	As long as 24 hours

NOTE: In 6 patients treated with oral stilbestrol, 0.1 to 1.0 mg. q.d., the cervical mucus did not change from the type found in the untreated menopausal patient.

The results in all cases are summarized in Table VII. The untreated patients uniformly showed scanty, cellular, tenacious mucus. Patients treated with small oral doses of stilbestrol showed, as a rule, increased amounts of mucus with higher pH and fewer cells, while those receiving 1.0 or more of stilbestrol per day and those implanted subcutaneously with estrogenic pellets showed the maximal change with abundant, flowing mucus which was glairy and transparent with a high pH, and almost no cellular elements. Several of these latter patients actually complained of "leucorrhea," and in each case examination showed the offending discharge to be mucus only. It is significant to note that in 6 other cases, given oral doses of stilbestrol varying from 0.1 to 1.0 mg.

per day, no change occurred in the cervical mucus though these patients improved clinically. In general subjective improvement corresponded with changes in the cervical mucus but exceptions did occur.

SUMMARY AND CONCLUSIONS

Four objective methods for determining the adequacy of estrogen therapy in the menopause have been considered for the purpose of evaluating their clinical usefulness. Our data, in agreement with reports of others, show that, in general, menopausal patients have little if any estrogenic substance in the urine, have increased amounts of gonadotropic hormone in the urine, show atrophic changes in the vaginal smear, and secrete a scanty, viscid, cellular mucus from the cervical glands. In patients adequately treated with estrogens the urinary level of estrogenic substance usually rises to the levels found in menstrual life; the urinary gonadotropic hormone often decreases or disappears; the vaginal smear typically changes to the estrous type; and the cervical glands secrete abundant, clear, alkaline, acellular mucus. However, we have also shown that the asymptomatic patient may still show objective evidence of estrogen deficiency and that the patient with symptoms may show evidence of estrogen activity. Though these cases are exceptions, they are also numerous. Therefore, we do not believe that the amount of estrogen necessary to increase the urinary output of estrogen to normal levels, to depress the elaboration of gonadotropic hormone, to change the vaginal smear to the estrous type, or to stimulate the activity of the cervical glands, is necessarily the same amount of estrogen that will be required to alleviate the vasomotor symptoms of the menopause.

While not intending to minimize in any way the value of these tests in investigative work, it is our opinion that in the regulation of estrogen therapy for the individual patient they are not sufficiently dependable to serve as crucial criteria, but should rather be looked upon as supplemental aids. We agree with Novak[22] who says, "On the whole . . . [the] vasomotor symptoms offer the best criterion as to the severity of the climacteric and as to the efficacy or inefficacy of therapeutic measures."

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THE DIAGNOSIS AND TREATMENT OF CARCINOMA OF THE CORPUS UTERI BASED ON EXPERIENCES AT THE WOMAN'S HOSPITAL*

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A PRESENTATION of the results of handling a large group of cases in a single institution in accordance with accepted methods of treatment, together with a careful follow-up study, is of value and importance. A comparison with the results of other operators in the same field adds to the interest of such a presentation.

The series at the Woman's Hospital includes 192 cases of corpus carcinoma observed during the period from 1919 to 1941 inclusive.

CLASSIFICATION

We follow the classification proposed by Ewing, who divides endometrial cancer histologically into four grades:

Grade I: Superficial papillary adenoma malignum
Grade II: Adenoma malignum
Grade III: Adenocarcinoma
Grade IV: Diffuse anaplastic carcinoma

Grade I is of low malignancy, while Grade IV is very malignant, anaplastic, and consequently radiosensitive.

Usually cancer of the corpus tends to produce the type of cell from which it arises, hence columnar epithelium and gland formation result, while the type of cell in cancer of the cervix is usually of the squamous variety. Occasionally corpus carcinoma may be composed of both cylindrical and squamous epithelium, and it is then designated as adenoacanthoma. This type is rare and metastases are more frequent,

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therefore the prognosis is not as favorable. It does not respond as well to radiation, so that an operation is most important.

In our series, 11 were classified as adenoacanthoma of which 3 survived five years or longer.

SYMPTOMS

Metrorrhagia, spotting, or a blood-tinged watery malodorous discharge is the predominant symptom, as it occurs in 95 per cent of the cases.

Postmenopausal bleeding, especially after a year, is always important as, with a normal cervix, two-thirds of the cases are of malignant origin.

Pain is usually absent except in the late stages and is an index of extension of the disease.

DIAGNOSIS

Microscopic examination of the growth is essential for diagnosis, thus a curettage is necessary to procure the tissue.

John Clark has pointed out that the passage of a uterine sound produces profuse bleeding, which would be absent in normal cases.

The method developed by Papanicolaou in his work at the Woman's and New York Hospitals for the diagnosis of carcinoma of the uterus by a study of the vaginal smears may be of value, if it proves to be accurate in early cases, but it requires the services of a trained cytologist to correctly interpret the findings. A recent report by Papanicolaou and Traut[3] described the method is of great interest.

PROGNOSIS

The Grades I and II, adenoma malignum type, give a high percentage of cures if treated in the early stages of the disease. In Grades III and IV the prognosis is more grave, depending upon the duration and extent of the growth.

The prognosis is contingent upon an early diagnosis and a prompt and adequate treatment. The time lost before the patient seeks relief for the irregular bleeding or discharge has been estimated to average between seven and eleven months. Valuable time is often wasted in patients with bleeding associated with fibroids due to an incomplete diagnosis of a co-existing carcinoma of the corpus uteri.

As an aid to prognosis, Healy has suggested dividing the cases into clinical groups according to the extent of the disease as shown by the increased size of the uterus.

Group I, The uterus is normal in size, with a depth of 3 inches. Has the most favorable prognosis.

Group II, A moderately enlarged uterus, 4½-inch depth, size of two and one-half month pregnancy. Intermediate as to hope of cure.

Group III, A markedly enlarged uterus 5 inches or more in depth, size of three month pregnancy. Is much less favorable for a cure.
Group IV, Extension of disease beyond the uterus. Is the least favorable type.

The statistics of Healy, Norman Miller, and others show generally a better prognosis in small- or normal-sized uteri.

TREATMENT

The ideal treatment for corpus carcinoma is a prompt total hysterectomy with salpingo-oophorectomy, performed with a technique that insures prevention of spill or spreading of the cancer cells during the manipulation. As a preliminary diagnostic curettage is nearly always necessary, intracavitary radiation should be done at the same sitting to render the tumor cells inactive.

The hysterectomy should be done usually in from four to six weeks subsequently, after all reaction from the irradiation has subsided. After convalescence from the operation, deep x-ray therapy by the fractional method, such as the Coutard technique, should be given.

Unfortunately, as these patients usually are past the menopause age, 50 per cent (53.6 per cent of our cases) are poor operative risks on account of senility, obesity, cardiovascular disease, renal insufficiency, diabetes, or the extent of the disease. Thus irradiation therapy alone must be depended upon in these cases.

In patients with excessive obesity, x-ray therapy is ineffective, as it cannot penetrate sufficiently to deliver the necessary depth dose. In such cases intracavitary radiation is our only resource.

It is technically difficult to introduce radium applicators into the uterine cavity so that the entire area of the endometrium will receive adequate and uniform radiation, especially in a uterus with a large and irregular cavity. Such irradiation is unreliable, as shown by areas of residual carcinoma often seen in the excised uterus. Sackett[10] reports that in our series 1 out of 3 removed uteri showed persistent carcinoma after irradiation. Thus the results with radium alone are much less favorable than when combined with hysterectomy.

Much attention has been given by various workers to devise a satisfactory method of distributing the radium adequately to the entire area of the uterine cavity.

In small- or normal-sized uteri the usual method is to introduce the radium capsules in tandem formation. Owing to the triangular shape of the cavity, this technique may fail to reach the cornua, as capsules in single tandem cannot reach all portions of a Y-shaped cavity if it is enlarged. Schmitz[6] devised a Y-shaped radium container for this purpose.

Heyman[7] packs the uterine cavity with a number of small specially designed radium cylinders until it is filled. This technique requires a large number of small units, which are difficult to apply and to remove.

Crossen[9] has devised an ingenious method of placing the capsules and holding them in the required position by means of wires. His article should be consulted for the details of the technique.

These methods all require accurate measurements of the size and shape of the uterine cavity. Heyman stresses the great caution necessary in applying his method, and states that perforation of the uterus is unavoidable in a number of cases. To avoid difficulty in removing the capsules he places a glass drain in the cervix to prevent contraction. He gives two treatments, averaging 1,500 mg. hours each, given three weeks apart. He does a hysterectomy only if symptoms reappear.

At the Woman's Hospital in every case of potential carcinoma of the corpus, a careful preoperative study of the patient is made, which includes a urologic and proctoscopic examination, blood study, and, in marked anemia or cachexia, a transfusion may be given. A diagnostic curettage is done under anesthesia. Care is taken to curette systematically and with gentleness the anterior and posterior wall and the cornua. Two 50 mg. capsules of radium element in tandem formation with 1 mm. of platinum and rubber screening are inserted to the fundus and anchored by suture through the cervix and vulva, a self-retaining catheter is inserted to keep the bladder empty, and the curettings are sent to the laboratory for a six-hour report (paraffin section). If the diagnosis is "benign," the radium is left in place for a period in accordance with the requirements of the case. If "malignant," a dosage of 2,400 to 4,000 mg. hours is given. A complete hysterectomy and bilateral salpingo-oophorectomy are done in from four to six weeks later.

In certain cases when the patient is not cooperative, we may do the hysterectomy earlier than four weeks after radiation. We have not encountered any unusual difficulty by so doing.

After convalescence is established, the patient receives a series of deep x-ray therapy by the Coutard technique.

I do not believe it wise to give preliminary x-ray therapy by the fractional method before the hysterectomy on account of the loss of valuable time, except in cases where the disease has extended outside the uterus and a hysterectomy is not feasible. Such a course would take a month and, with the delay associated with the intracavitary radiation, the hysterectomy would be delayed for over two months. Prompt surgery is the essential treatment and is vitally important.

In the technique of hysterectomy, the cervix should be closed by suture, both tubes should be clamped on opening the abdomen, and clamps placed down each broad ligament to prevent dispersal of carcinoma cells as a result of the manipulation. The technique of Worrall[12] and Lahey,[13] or that of Richardson[14] or Farrar[15] is most efficient for a safe operation and for giving adequate support for the upper pelvic floor.

In the inoperable cases, we believe repeated intrauterine radiation is advisable, with a dosage of from 2,400 to 4,000 mg. hours at four-week intervals, depending on the size of the uterus and the result obtained. Whenever feasible, deep x-ray therapy should precede or follow the intracavitary treatment.

Heyman has called attention to the group of cases in which both the cervix and the corpus uteri are involved. He classifies them as "*cancer corporis et colli uteri.*"

In my opinion these cases should be treated as cancer of the cervix.

RESULTS

It is of interest to review for comparison the results recently reported from some of the larger clinics.

An analysis of our results at the Woman's Hospital in cases of corpus carcinoma seen from 1919 to 1935 and followed for five years or longer is presented in Table I. This shows that of a total of 142 seen, 63 survived five years or more, or an absolute rate of 44.4 per cent. Nine were untreated. One hundred thirty-three were treated, with a relative survival of 47.4 per cent. Of those treated by surgery alone there were 27, of whom 17 survived five years, or 63 per cent; by irradiation alone, 69 (operation contraindicated in 37, or 53.6 per cent), 22 survived 5 years, or 32 per cent; by irradiation and surgery 37, 24 survived five years, or 64.9 per cent. Untraced counted as "dead of cancer," 1 case. Two patients refused operation after irradiation. Our primary mortality in operative cases was 3.2 per cent.

TABLE I. FIVE-YEAR END RESULTS, CARCINOMA CORPUS, JAN. 1, 1919, TO DEC. 31, 1935

	TOTAL	LIVING 5 YEARS	SURVIVAL RATE PER CENT	
Total seen	142	63	Absolute	44.4
Untreated	9	0	0	
Treated	133	63	Relative	47.4
Surgery alone	27	17	Relative	63.0
Radiation alone*	69	22	Relative	32.0
Radiation and surgery	37	24	Relative	64.9
Untraced, counted as dead of carcinoma, one case				

*Operation contraindicated in 37 (53.6 per cent). Two refused operation after irradiation. In the others, the disease was inoperable.

In my opinion, in view of the more frequent association of carcinoma with fibromyoma (35 to 40 per cent), it is best to remove the entire uterus in all such cases when there is no probability of serious increased risk, and the removed specimen should always be opened at the time of operation unless a carcinoma of the corpus be overlooked.

Complications in the inoperable group, such as pyometra, perforation, and rectal and intestinal stricture are not infrequent.

Heyman's last report in 1941 (cases from 1914 to 1934 inclusive) is as follows:

Total cases seen	416
Not treated	14
Treated radiologically	402
Alive five years with no evidence of disease, absolute rate 45.7%, relative rate 47.3%	
Total alive five years (salvage)	51.74%

By Heyman's multiple packing method, used since 1934, he reports a four-year survival of 75 per cent. He appears somewhat reluctant to give up radiation alone, as he advises hysterectomy only after radiation has failed, and wishes to postpone judgment as to the advantages of hysterectomy *versus* radiation alone in frankly suitable operable cases.

Masson and Gregg[16] reported, in 1940, the results from the Mayo Clinic. In twenty-four years, 732 cases were seen and 728 patients were treated with radiation alone; a five-year survival relative rate of 59.5 per cent was obtained. Operation with and without radiation gave a relative rate of 73.1 per cent. Their five-year survival rate of 711 traced patients was 59.8 per cent.

Healy and Brown,[4] in 1939, reported seeing 283 cases in fifteen years, of which 86 were previously treated. Seventy-eight per cent were postmenopausal. One hundred ninety-seven received primary treatment, with a five-year survival of approximately 48 per cent. Ninety-six were treated with radiation alone with a five-year survival of 39 per cent. Ninety-three were treated with radiation and surgery with a five-year survival of 55 per cent. Eight were treated with surgery alone. In a small group of 28 patients treated by their later technique, using 3,000 to 4,000 millicurie hours of radon, they had a survival of 79 per cent. Their average technique comprises curettage, intracavitary radiation of 3,600 millicurie hours, then a deep x-ray series, and six to ten weeks later a complete hysterectomy. His operative mortality was 4.3 per cent.

Norman Miller,[17] in 1940, reported 183 cases seen, 156 treated, 71 by irradiation, 10 by operation, and 75 by irradiation and operation. Of this series, 68 were eligible for a five-year survival study:

Irradiation 29 (five-year survival)	34.4%
Operation 5 (five-year survival)	80.0%
Irradiation and operation (five-year survival)	70.5%
Absolute five-year survival rate for all	52.1%
Operative mortality rate	3.5%

Miller advocates preliminary deep x-ray therapy before operation.

As a curettage is necessary for a diagnosis in nearly all cases, intracavitary radiation at the same sitting saves precious time, and is I believe of more proved value than x-ray therapy, which should follow hysterectomy.

SUMMARY

1. Early diagnosis gives the best chance for a cure.

2. A diagnostic curettage is most important in all cases of persistent bleeding, especially at or after the menopause, to determine the presence of malignancy.

3. Clinical grouping based on the size of the uterus as an aid to prognosis suggested by Healy is of value; a small- or normal-sized uterus has a better prognosis.

4. The ultimate prognosis depends upon the age, physical state of the patient, duration of symptoms, extent of the disease, a prompt diagnosis, and the type of treatment.

5. A diagnostic curettage and intracavitary radiation, total hysterectomy and bilateral salpingo-oophorectomy, and deep x-ray therapy is the ideal treatment and gives the best results.

6. Total hysterectomy should be the operation of choice in fibroid cases whenever feasible.

7. Operable cases of corpus carcinoma treated by irradiation, surgery, and x-ray should average 70 per cent five-year survival.

8. Inoperable cases with irradiation alone should show an average five-year survival of 35 per cent.

9. In inoperable cases the technique devised by Heyman and that of Crossen hold promise of giving improved results.

10. Irradiation alone has a definite cure value.

11. Each patient with carcinoma of the corpus uteri must be individualized and treated according to the conditions present to obtain the best results.

12. The early prompt removal of the uterus, tubes, and ovaries is the most essential factor in the treatment of carcinoma of the corpus, irradiation being a valuable adjunct.

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CLINICAL, PSYCHIATRIC AND PSYCHOANALYTIC STUDY OF A CASE OF MALE PSEUDOHERMAPHRODITISM

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THIS report deals with a case of male pseudohermaphroditism. In using the term "male pseudohermaphroditism" we are applying the terminology used by Young.[1] By "pseudohermaphroditism" this author refers to a condition in which the sex glands are entirely male or entirely female while the external sex characteristics are partly or wholly those of the opposite sex. "Male pseudohermaphroditism" according to Young is a condition in which the sex glands are male in spite of the presence of many female secondary sexual characteristics.

The present case was studied clinically and the diagnosis was established by laparotomy and by microscopic examination of the biopsy material. Hormonal studies were carried out. The patient was also studied psychiatrically and, in order to obtain more complete data, a psychoanalysis was carried on for six months. Similar cases have been previously reported.[2] To our knowledge this is the first case of verified male pseudohermaphroditism studied psychoanalytically.

CASE HISTORY

A 17-year-old, white, single patient (S. M., Unit No. 35209) was admitted to the Massachusetts General Hospital complaining of absence of menses and failure of her breasts to develop. The patient had always considered herself a female, physically and mentally healthy, and the equal of companions of her own age. The only abnormalities, in the patient's opinion, were the absence of menses and lack of breast development.

Summary of History.—There was no familial history of mental disease or of hermaphroditism. The patient had a normal early development. During childhood she had measles, mumps, chicken pox, and scarlet fever. She had no other serious illnesses or operations. Her mother died following childbirth when the patient was nine years old. During childhood she had been a nail biter, had frequent crying spells, and was easily frightened. There was no history of eneuresis or of other neurotic traits. More recently the patient noticed that she had a headache, a lump in the throat and palpitation whenever she was frightened, nervous, or excited. Rare dysuria had been present for three or four years. The patient stated that she had not had any menstrual flow and had noticed the lack of development of breast tissue.

School History.—The patient started to school at the age of five and at seventeen she was in the eighth grade. She was kept out of school a great deal because of sickness and frequent change in residence. She was an average student, liked all of the subjects but showed a preference

for drawing. After leaving school she obtained a position as a nursemaid which she held until the present hospital admission.

Sex History.—During childhood and adolescence her interests were always feminine. She was interested in dolls, fine dresses, and in playing house. In games she always assumed the feminine role. During puberty she showed interest in boys, went to dances, and here too assumed the conventional feminine role. She became interested in one boy with whom she had some intimate experiences but which never led to attempts at intercourse. Later on she became interested in sewing, cooking, and in housework. In her work as a nursemaid she stated that she enjoyed dressing babies and had typical phantasies of being married and having a family. She preferred little girls to boys, stating that she enjoyed dressing girls in fine clothes. The absence of menstrual periods and the lack of breast development made her feel at times that she could not get married and have children. She could not resign herself to this state of affairs and was in hopes that she could become a normal girl.

Personality.—The patient stated that she was usually happy; readily made friends with both sexes. She liked to go out socially, and preferred not to be alone. Her range of interests was limited. She was not religious and had no special hobbies. She read some and stated that she did not like love stories. At times she was not truthful. On the whole she seemed to be an outgoing, dull person, with a moderately low intelligence.

Physical Examination.—Physical examination disclosed a young, white adult whose general body contour was that of a thin boy. The shoulders were fairly wide; the thorax was thin; and the pelvis was narrow. The extremities were fairly long with large hands and feet. The hands appeared large boned, the fingers large knuckled and blunt, and the skin was rather coarse and had large pores. There was an acneform eruption over the surface of the arms and upper back. The scalp hair was light brown, straight, and of fine texture. There was a very fine blond mustache; a few hairs were present under the chin but there was no beard. The axillary hair was sparse; pubic hair was female in distribution; there was slight hypertrichosis of the legs. The head showed no gross bony abnormalities. The supraorbital regions were large, and there was a palpable laryngeal prominence. The voice was deep and definitely boyish in quality. The thorax had a shallow anteroposterior diameter and tapered downward with a narrow acute subcostal angle. No mammary tissue was present. Examination of the heart, lungs, and central nervous system revealed no abnormalities. The blood pressure was 140/70.

Pelvic Examination.—There was a small mons veneris present. The most striking thing about the examination of the external genitals was the presence of a large clitoris, so large that it could easily be called a small penis (Fig. 1). The measurements were 3 cm. in length and ¾ cm. in diameter. A fairly good prepuce hooded the glans and the structure was more clitorislike than penislike except for its size. Erectile tissue was present in the clitoris. There were good-sized labia majora and small labia minora. The vagina was only a dimple such as is seen in young girls who have no vaginal canal. The urethra was separated from the clitoris or penis and in the usual position of the female urethra. No testicles could be felt in the vulva or in the inguinal canal.

Laboratory Examination.—Hematologic and urine examinations were within normal limits. Blood Hinton and Wassermann were negative. Phenolsulphonephthalein excretion was within normal limits. Electrocardiogram in recumbent position showed no abnormalities.

Hormonal and Related Studies.—Two examinations before operation for the presence of 40 mouse units per 100 c.c. of follicle-stimulating hormone were negative. These assays were carried out on nonconcentrated urine. Two determinations for androgenic substances showed the presence of 28 international units per twenty-four hours.[3] The serum calcium was 9.7 mg./100 c.c. and the total cholesterol was 165 mg./100 c.c. The sugar tolerance curves were within normal limits both before and after the operation. Intravenous pyelogram showed normal size and shape of the kidneys and normal excretion of dye. X-rays after an adrenal air injection showed no evidence of enlargement of adrenals. X-rays of the skull showed no abnormalities.

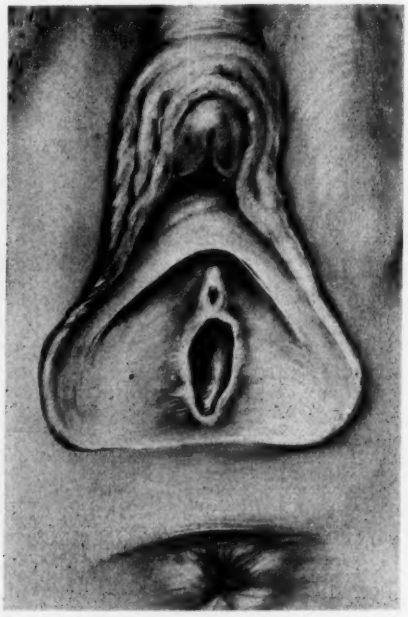

Fig. 1.—The vulva, labia, underdeveloped vagina and the large clitoris.

After the laparotomy, examinations were made for the presence of follicle-stimulating hormone, androgenic and estrogenic substances. Five determinations of follicle-stimulating hormone were made. On Feb. 7, 1938, the test was positive for 66 mouse units per 100 c.c., negative for 100 mouse units per 100 c.c. On Feb. 28, 1938, it was positive for 40 mouse units per 100 c.c. and negative for 67 mouse units per 100 c.c. On March 21, 1938, it was positive for 67 mouse units and negative for 100 mouse units per 100 c.c. These assays were carried out by direct injection of straight urine after acidification with acetic acid to a pH of 5.0 and shaking with ether. Another determination on Dec. 12, 1938, was positive for 20 and negative for 50 mouse units per 100 c.c. The latest determination on Dec. 20,

1938, was positive for 30 mouse units and negative for 50 mouse units per 100 c.c. The last two assays were carried out by precipitation and concentration on follicle-stimulating hormone by the tannic acid procedure. The recovery of follicle-stimulating hormone was not complete and the lower values are probably due to the incomplete recovery. These studies show that there was an increased excretion of follicle-stimulating hormone following the operation. The quantity of this hormone excreted is in excess of what one would expect to find in an individual with active gonads secreting adequate androgen or estrogen. The amount of follicle-stimulating hormone secreted by this patient is of the range usually found in castrates and in individuals during and after menopause. After the operation one determination showed the presence of 120 mg. of C17 ketosteroids (method of Callow).

Fig. 2.—The female type of pelvis as seen at laparotomy, showing absence of all female pelvic organs.

Mental Status.—The patient was slovenly in appearance, her hair was stringy and disorderly; her complexion was poor. She used lipstick and red fingernail polish. She smiled rather easily, occasionally in a silly, sly fashion but never inappropriately. The patient seemed very shy and not at all talkative. There was no abnormality of mood and no evidence of hallucinations, delusions, or paranoid ideas. The patient was well oriented for time, place, and person. Her memory was good in all modalities and her grasp of information was below normal. The I.Q. was 74.

Operation.—A laparotomy was performed on May 29, 1937. The liver, spleen, and gall bladder were normal. The kidneys were both present and of normal size and in the normal position. The appendix was found in its proper position and was removed. Inspection of the pelvis

showed a large cavity, much more female than male (Fig. 2). There was no uterus, tubes, or ovaries. No evidence of Müllerian duct formation was present. No prostate or seminal vesicles could be located. Two cords were seen running from the internal ring down behind the peritoneum and ending blindly in the region of the absent prostate. These were taken to be vasa deferentia and were of such good size that it was considered proof that testicles were to be found somewhere. On palpating the inguinal canals with a finger in the abdomen and one on the skin, two testicles were found high in the canals. Incisions were made in the skin over these gonads and they were brought out of their beds. They were normal in every respect: color, size, and consistency. Sections were removed from each for histologic study. The sections were

Fig. 3.—Photomicrograph of nonsperm forming testes. Notice large number of large cells (cells of Leydig) in the supporting connective tissue.

taken from the cortex in the long axis and comprised about one-sixth of the testicular structure. The incisions in the testicles were then closed, and also the skin of the inguinal canals. The abdominal incision was closed in the usual manner.

Microscopic Examination of Biopsy Material.—Examination of the removed tissue by the pathologist showed well-formed tubules that were lined by a three to four cell deep layer of epithelial cells completely devoid of mitotic figures (Fig. 3). No spermatozoa were present. Large numbers of polygonal cells of good size were present in the connective tissue septa. These septa were larger and wider than usual. The polygonal cells had eccentric round nuclei and abundant brilliantly acidophilic cytoplasm and were considered to be Leydig cells. These were far more numerous than are seen in a normal testicle. In one area a small collection of cords without lumina was present, suggestive of an undifferentiated stage of testicular development. The testicle was considered to be nonsperm-producing and therefore nonfunctioning as far

as spermatozoa were concerned. However, the large number of interstitial or Leydig cells suggested active function on the part of the organ secreting androgens.

Summary of Psychoanalysis.—The earliest memory which the patient recalled was an episode at the age of four in which she was taking the female role while playing with dolls. Her earliest impression of her father dealt with ideas of her father's cruelty and her mother's drudgery. The patient identified herself with the mother. Later material indicated a shift in her attitude to one of rivalry with the mother. The death of the mother in childbirth when the patient was nine years old emphasized the cruelty and dread of the father and led to the idea that the father would beat and maltreat the patient just as he had her mother. It seemed that from this point in her life she remained identified with her mother, and developed anxiety in relation to her father. There were several anxiety dreams which the patient had dealing with fear of her employer and fear of operations. These dreams associated directly to memories of scenes in which the patient felt that her father would injure her just as he had beaten the mother.

Later phantasies indicated that she had transferred her fears to other men, and the idea she clung to even up to the present was that men are cruel, unreliable, and are not to be trusted. There was a great deal of introspection as to what role the father could have played in the death of the mother, and she attempted during early adolescence to find out details of the mother's death, and of the place where her mother was buried. Her lack of menses emphasized her inferiority. This material was invariably associated with ideas of being injured.

Her interests in clothes and in men became more marked during adolescence. With considerable difficulty she described her conflict in relation to men. Eventually she described her overt sex activities with her "boy friend" and indulged in masturbation with typically feminine masturbation phantasies. These concerned her friend and later concerned the analyst.

In brief, the psychoanalytic material concerning her emotional development and phantasy life was quite typical of that found in females. The details of the psychoanalytic material will be reported elsewhere.

COMMENT

Our studies on this patient indicated that from the anatomic point of view we were dealing with a person having preponderately masculine characteristics (presence of hirsutism, shape and contour of the body, presence of rudimentary penis, presence of nonsperm-producing undescended testes, absence of breast development and absence of uterus, tubes, and ovaries). The female structures present were labia majora and minora, female type of urethra and a rudimentary vagina. From the hormonal point of view the preoperative studies indicated a normal absence of an increased excretion of follicle-stimulating hormone.

From an endocrine point of view this patient is apparently a normal male except for cryptorchidism. Because of nondescent of the gonads, spermatogenesis has been interfered with, since for the completion of spermatogenesis a temperature lower than that of the body is necessary. The high excretion of follicle-stimulating hormone in the urine is an expected finding in cryptorchidism.[4] Just why the two follicle-stimulating hormone tests before operation did not show excretions of

follicle-stimulating hormone greater than 40 mouse units per 100 c.c. of urine while those after operation did, is not quite clear. It is possible that the preoperative urines were more dilute. The 17-ketosteroid excretion was within normal limits and requires no comment. The androgens as determined by biologic assays were slightly low; whether this is the usual finding in cryptorchidism the authors do not know.

From the behavior point of view this individual with predominately masculine structure and the above hormonal picture was reared as a female, had feminine interests, and passed as a female. The psychoanalytic study indicated the patient's early emotional development was typical of that found in females.

We believe that this study offers presumptive evidence that the eventual development of the female did not at all go hand in hand or correlate with the structural and glandular picture. The presumption is that factors other than the anatomic and glandular ones played the predominating role in the emotional and psychosexual development. What these other factors are is at present not clear. However, it is of interest and significance that this status can exist in an individual. This study would indicate that broadly speaking the environmental and situational factors (reared as a girl, identification with mother, relationship to father, etc.) in this patient played the predominating role in her psychosexual and emotional development.

During the operative procedure it was decided that the testicles should not be removed. It was felt that the excision of the testes might bring about a sudden cessation of hormones and might bring about a "menopause" with its attending symptoms. The testes were left in as androgenic hormone produced by them should prevent castration symptoms. It was decided eventually to give the patient large doses of estrogenic substances to stimulate breast development and later to attempt a plastic operation for the formation of a vagina.

SUMMARY

A case of pseudohermaphroditism was studied clinically, psychiatrically, psychoanalytically and from the hormonal point of view. Structurally the patient was preponderately a male with nonsperm-producing testes. The hormonal studies showed an increased urinary excretion of follicle-stimulating hormone after laparotomy and biopsy of the testes. This increased excretion of follicle-stimulating hormone was not present before operation. The urinary androgens were well within the normal range for males and females. The psychiatric and psychoanalytic studies indicated that the patient had an emotional and psychosexual development typical for females.

The authors wish to express their thanks to Dr. Fuller Albright for his critical evaluation of the endocrine findings and also to Dr. R. I. Dorfman, Yale University School of Medicine, New Haven, Conn., for his determination of androgenic substances.

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DEATH DUE TO INTRAPERITONEAL RUPTURE OF A STRICTURED LYMPHOGRANULOMATOUS RECTUM DURING PARTURITION

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FORTUNATELY, there is a high degree of sterility in women suffering from lymphopathia venereum. This disease, especially in its late stages with rectal stricture, is a serious complication of pregnancy and causes the obstetrician grave concern in his choice of method for delivery. A narrowed rectal canal which is just adequate in the non-pregnancy state, may become almost occluded with the edema which occurs due to increased venous and lymph stasis of the pelvic viscera during pregnancy. Dilatation of the colon with varying degrees of debilitating colitis often results. Added to this is the trauma to the rigid rectal wall in delivery via the vaginal route and a stormy puerperium with severe, almost intractable, distention may be expected. Even cesarean section does not always obviate severe distention and a stormy convalescence.

In the Sloane Hospital for Women on the obstetric service there have been 7 proved cases of lymphopathia venereum in the past four years. During this time there were 6,497 births. Of these 7 cases, 3 were delivered of premature 7½ months' babies spontaneously; 1 at full term spontaneously; 2 by cesarean section, one of which also had a permanent colostomy done at the same time. One of the section cases had had a severe bout of debilitating colitis in her seventh month, which fortunately yielded to conservative therapy and her puerperium was uncomplicated. One case terminated fatally for mother and infant and will be reported in detail. (One case of pregnancy with rectal stricture due to lymphopathia venereum further complicated by fibroids was terminated in the fourth month by hysterectomy and is not included in this group.)

CASE REPORT

J. T., 32-year-old negro housewife, grav. ii, para i, whose only child, born seven years previously, died at the age of three months, cause unknown, had registered in Sloane antepartum clinic well in the third month of her present pregnancy and had insisted on continuing it despite her being advised against doing so. She had had a positive Frei test in October, 1937, at which time the Wassermann was negative, and

she had received intermittent treatment in the Vanderbilt Clinic for three and one-half years, for her rectal stricture, with indifferent success. Her symptoms of intermittent rectal bleeding dated back ten years. The rectal canal was 0.4 cm. in diameter. Her past history also included typhoid fever in childhood and an appendectomy with drainage in 1921.

Her ante-partum course was uneventful; the pelvis gynecoid. She was admitted to the labor room two weeks before her expected date of labor, having just ruptured her membranes and having painless contractions. Upon pelvic examination the breech was presenting and a twelve-inch loop of pulsating cord had prolapsed into the vagina. This was replaced under anesthesia and a No. 3 Voorhees bag was inserted into the uterus. The fetal heart remained normal, about 140 per minute for one and one-half hours, following which it became feeble, irregular, and then ceased to be heard so the bag was removed. Desultory pains began on the insertion of the bag and continued somewhat stronger after its removal. She was given an enema at this time, nine hours after admission, with good returns of fecal fluid. Another enema one hour later returned fecal fluid and formed stool. She was delivered, after eight and one-half hours of fair labor, of a stillborn infant by easy assisted breech delivery with slight suprafundal pressure for delivery of the head. Immediately following delivery and for two hours afterward her condition appeared good. Four hours after delivery, however, she began to complain of cramplike abdominal pains which were thought to be afterpains and which were relieved by aspirin and luminol. Her abdomen, however, gradually became more distended and she continued to complain of generalized abdominal pain with increasing abdominal tenderness.

Ten hours after delivery a rectal tube was inserted and a flaxseed poultice was applied with little relief of the distention. Seven hours later she was thought to have early peritonitis and, when the rectal tube was removed, it contained some bloody discharge. An enema was given at this time with no return. One hour later one of the nursing staff noted slight cyanosis of the patient's lips but was not alarmed and did not call the house physician until her pulse became feeble and later imperceptible. She did not rally and was pronounced dead twenty-one hours after delivery. Permission for autopsy was obtained.

EXTRACT FROM AUTOPSY RECORD (NO. 13,623)*

About 1,500 cm. of thin, cloudy, blood-tinged fluid with flecks of fibrin was present in the abdominal cavity. The gastrointestinal tract was tremendously distended with gas. The transverse colon and the splenic flexure were filled with a hard firm mass of feces. The peritoneal surfaces of the pelvic viscera were covered with a fibrinopurulent exudate. The uterus was enlarged and reached up out of the pelvis. Several small myomas of the uterus were present. There was nowhere any perforation of the genital organs.

The rectum had been completely separated into two pieces, 2 cm. below the proximal end of a stricture, which, 10 cm. in length, affected the terminal part of the rectum. The proximal end of the rupture of the rectum was separated by about 10 cm. from the distal end. The rupture was an intraperitoneal one (Fig. 1).

*The autopsy was performed by Dr. Robert C. Horn of the Department of Pathology.

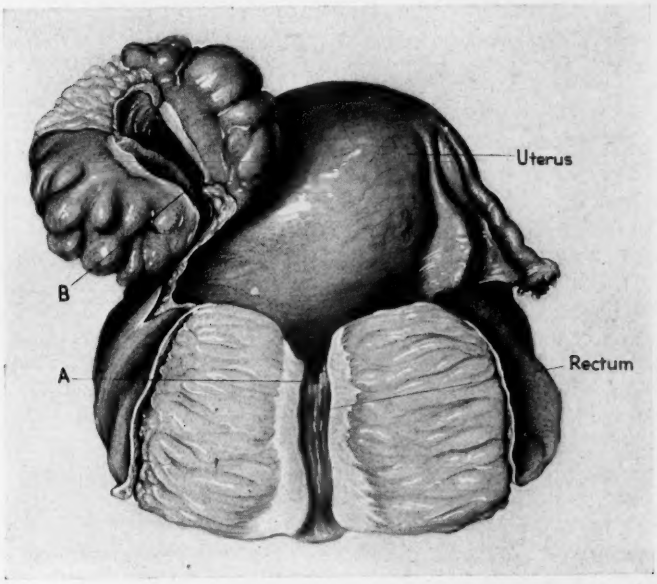

Fig. 1.—Rupture of rectum due to lymphogranuloma venereum.

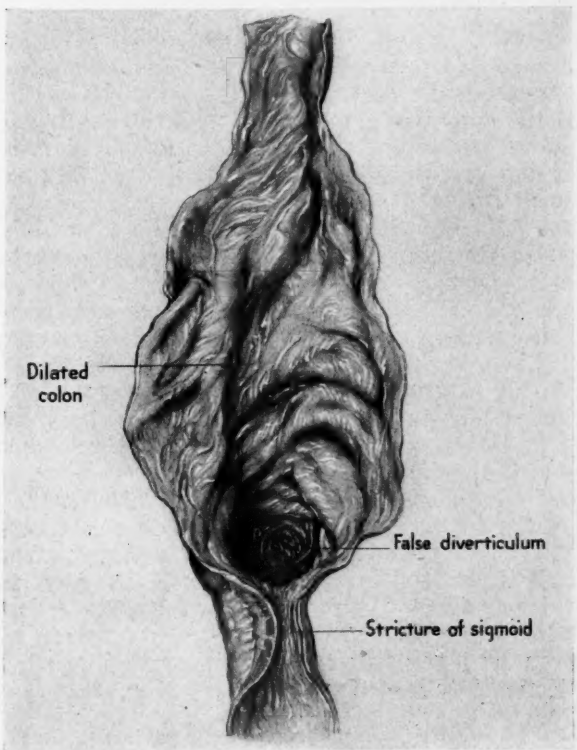

Fig. 2.—Stricture of sigmoid colon with a diverticulum above.

Seven centimeters above the stricture of the rectum, the sigmoid colon showed a sharp narrowing of the lumen, over a distance of 3.5 cm. Just above this stricture a wide-mouthed false diverticulum 7.5 cm. deep had been formed. The sigmoid colon showed extraordinary dilatation and thinning of the wall (Fig. 2).

The strictured portion of the rectum had an internal circumference of about 2 cm. The constriction at the point of the rupture was slightly more marked than elsewhere.

A bolus of feces was impacted in the sigmoid immediately above the stricture of the rectum. An extremely large mass of feces in the sigmoid colon proximal to the second stricture was present. The internal circumference of this stricture was 2.5 cm.

The epithelium of the distal part of the rectal stricture appeared gray, glistening, and thick, above this, granular.

The edges of the tear were rounded and covered with pink and gray granulations. There were also a few areas of hemorrhage. The muscularis was thick and firm. A disproportionally large mass of rather firm adipose tissue with streaks of fibrous tissue surrounded this portion of the rectum.

The mucous membrane of the strictured sigmoid colon was granular. The muscle was thickened and fibrin was present in the surrounding fat tissue.

HISTOPATHOLOGY

Rectum.—The microscopic findings were characteristic for lymphogranulomatosis with stricture of the rectum: cell infiltrations, especially of eosinophiles and plasma cells, in the mucosa, submucosa and muscularis, also in the walls of the vessels; thickening of the connective tissue and of the muscularis; necrosis of the cell infiltrations, thickening of the subperitoneal fat tissue; dilatation of the lymphatics and narrowing of the smaller and greater vessels by thickening of their intima and media.

The mucosal epithelium was either squamous or atrophic or ulcerated.

Peculiarities of the autopsy findings were the extensive local changes of the vessels in a person only 32 years old, without any alterations of the coronary arteries and with only slight thickening of the aortic intima.

Fibrosis of the muscularis mucosa and rupture of the elastic tissue of the vessels and between the muscle tissue were striking.

At the point of rupture of the rectum, the atrophy of the mucosa, which was replaced by connective tissue and hemorrhages, was extreme.

A striking finding was a hemorrhage from a thrombosed vessel far from the site of the rectal rupture.

Worth mentioning also was the bacterial invasion of the wall and of the interior of the vessels of the wall at the edge of the rupture.

Interesting renal lesions interpreted as lymphogranulomatous were present. Small interstitial groups of plasma cells were seen. In one area densely infiltrated by lymphocytes and plasma cells, a group of convoluted tubules were distended with granular debris in which nuclear fragments were present. The cellular infiltrate formed a suggestive papillar projection into one of these tubules (Fig. 3).

DISCUSSION

According to Yeomans,[1] rupture of the rectum may be the result of trauma or occur spontaneously. Impalement, bullet wounds, perforation

by bougies, enema tubes of the sigmoidoscope are such traumatic causes, as well as contusions by a kick or fall or other indirect violence.

Spontaneous ruptures may also be caused by sudden increase of intra-abdominal pressure as from violent vomiting, lifting heavy weights or severe straining at stool.

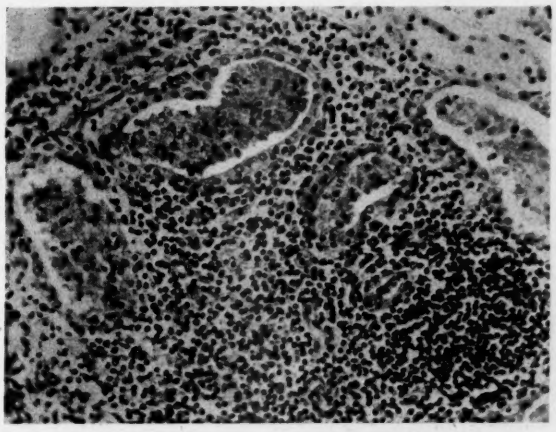

Fig. 3.—Kidney, rounded cell infiltration in cortex.

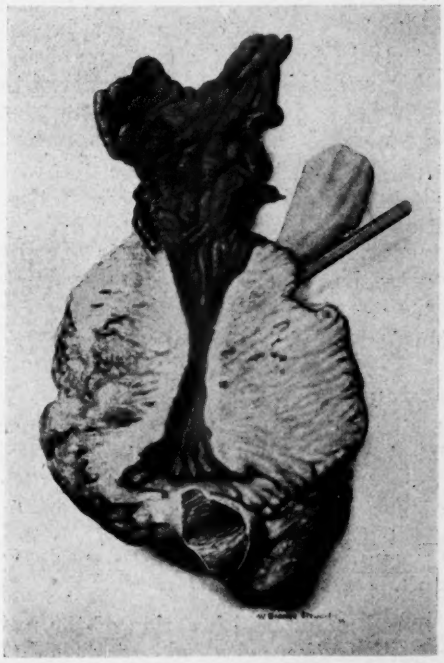

Fig. 4.—Shows a strikingly similar lymphogranulomatous stricture of the rectum with an ileosigmoidal fistula. The cause of death was peritonitis, probably due to perforation of sigmoid. (Case reported by Dr. L. Lichtenstein.)

Cases of spontaneous rupture of the healthy rectum have been reported by Heineke,[2] Christian,[3] Delbet,[4] Bunge,[5] and Burkhardt.[6] Burkhardt's patient was saved by an early laparotomy.

Traumatic rupture of the diseased rectum (for example during dilatation of a stricture) is of more frequent occurrence.

Warthen[7] and Bacon[8] cautioned against even digital exploration in such cases. Warthen combined colostomy with obliteration of the "cul-de-sac" to avoid the danger of dilatation.

Lichtenstein[9] published 5 cases of rectal stricture observed at autopsy. The cause of death in Case 3 was peritonitis, probably due to spontaneous perforation of the sigmoid with ileosigmoidal fistula (Fig. 4); in Case 4 a chronic ulcerated granulomatous proctitis with marked stenosis, decubital ulcers of the sigmoid with perforation and diffuse fecal peritonitis.

The case of Dorsett[16] and the case of Kassebohm and Schreiber[10] are the only two cases in the literature of rupture of a stricture of the rectum occurring at delivery. These strictures were probably due to syphilis. The case of Kassebohm and Schreiber[10] was complicated by a rectovaginal fistula. Our case is the first proved case of spontaneous rupture of lymphogranulomatous stricture of the rectum at delivery. The diagnosis "lymphogranuloma venereum of the rectum" has been established during life by a positive Frei test four years ago, by an elevated blood globulin, by biopsy of the strictured rectal tissue taken one year ago, which showed a lesion compatible with lymphogranuloma venereum and by the autopsy findings. What are the causes of this rupture? It seems probable that the strictures of the rectum and the sigmoid raised the interior pressure of the bowel because the upper part of the sigmoid must strain to expel the contents of the bowel. The extraordinary dilatation and thinning of the wall of the upper sigmoid favor this interpretation. The raised interior pressure caused the rupture, because the wall of the bowel was abnormal.

The contracting uterus may have tugged on the rectal wall. The expelling pains may have pressed the breech presentation against the most vulnerable portion of the wall of the rectum. This pressure may have been much raised because the room of the pelvis was already considerably narrowed by the extensive development of inflammatory tissue in the wall of the rectum.

Another question is, why is the rupture transverse and not longitudinal?

The rectum is a cylinder and its normal wall may have a uniform thickness. The strains or tensions by the interior pressure are doubly as great in the longitudinal direction as in the transverse one. We should then have expected a longitudinal rupture. Tensions of the wall may be raised by holes, notches, and sudden change in the direction of the wall. The ulcerated part of the wall could correspond to such holes and notches. Weakening of the wall and reduction of the elasticity could have furthered such a transverse rupture.

There has been found a bacterial invasion of the wall of the ruptured rectum. Whether the infection preceded or followed the rupture cannot be stated.

An interesting finding is rupture of a thrombosed vessel in the wall of the rectum, far from the site of the rectal tear. We raise, but cannot answer, the question whether this hemorrhage had anything to do with the origin of the rupture of the rectum.

That pregnancies may be successfully completed even in the presence of a lymphogranulomatous stricture of the rectum is shown by the cases cited above from the Sloane Hospital and by the following cases: Huet and Villars[11] have reported a case in which proctitis developed after pregnancy, necessitating a colostomy; lesions persisted during two succeeding pregnancies, terminating in complete stricture of the rectum. The Frei reaction was positive. The severe disease of the rectum did not cause any obstetric difficulty or hazard. Fagarasanu[12] has performed an intrasphinctereal and abdominoperineal resection of the rectum for stenosis in the second month of pregnancy. It was followed by the normal development of pregnancy and satisfactory results one year later.

Two particular features in the pathology of this case remain to be discussed:

1. The multiple type of the rectal stricture.
2. The lymphogranulomatous focus in the kidney.

1. Bacon is of the opinion that rectal strictures seldom extend above the level of the third sacral vertebra (posterior leaflet of peritoneum) and are usually single. Mathewson[13] found three types of stricture: (A) An annular stricture 1 to 6 cm. above the anocutaneous margin. This type is usually single, may be multiple. (B) A barrel-shaped stricture from 2 to 6 cm. long with smallest aperture proximally, distally ulcerated. (C) Diffuse involvement of the whole bowel distal to the pelvirectal junction.

Taylor[14] described a high stricture in the descending colon and another lower stricture in the rectum, in a patient with a positive Frei test. In both, the lumen was narrowed and the mucosa showed generalized ulceration. The cul-de-sac was normal. Our case is quite similar to his.

2. Interesting renal lesions in our case were interpreted as lymphogranulomatous. Reichle and Connor[15] first described follicular granulomatous lesions in the kidneys. The infiltration was in part in the glomeruli, but chiefly in the interstitium, and in places led to the formation of small abscesses. We have in our records another case (Autopsy No. 11,631) in which renal lesions, interpreted as lymphogranulomatous, were present. There was a positive Frei test.

Pathology of Fetus.—No lymphogranulomatous lesions were found, but merely early maceration with congestion and hemorrhages into the viscera.

SUMMARY

1. This is the first proved case of spontaneous rupture of a lymphogranulomatous stricture of the rectum at delivery.

2. It is possible, though it cannot be proved in our case, that the rupture was initiated by spontaneous hemorrhage in the wall of the rectum.

3. We believe that the pressure from within had much to do with the origin of the rupture.

4. The case is exceptional in that there were two strictures in the bowel, one in the rectum, and the other in the sigmoid; the lymphogranulomatous changes were more severe in the rectum than in the sigmoid.

5. We come to the conclusion that pregnancy and delivery increase the danger of rupture of a lymphogranulomatous rectal stricture. This

danger should indicate the advisability of early radical surgical treatment before pregnancy or in the earliest months of pregnancy. Furthermore, in the case of collapse or beginning peritonitis, during and after delivery of a patient with lymphogranulomatous rectal stricture, it is of greatest importance to suspect a rupture of the strictured rectum. Then surgical help would be immediate.

We wish to acknowledge our indebtedness to Drs. Kesten, Sproul and Horn for their friendly collaboration and to Dr. L. Lichtenstein for the permission to reproduce the photograph of his case (Fig. 4).

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ENDOMETRIAL CYST OF THE GROIN ASSOCIATED WITH A DECIDUAL REACTION IN THE APPENDIX

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THE occurrence of aberrant endometrial tissue in the groin was first described by Cullen[1] in 1896 and since that time a number of cases have appeared in the literature. The condition, however, is rare. In Counseller's[2] large series of 884 patients with endometriosis, no case was observed with endometrial involvement of the inguinal region and Polster, as cited by Hosoi[3] in a series of over 1,000 collected cases of endometriosis, discovered only 34 with involvement of the inguinal region. The total number reported at the present time is probably less than 50.

Much of the discussion in the reported cases has been devoted to the pathogenesis of the lesion. Five possibilities have been advanced to explain the occurrence of ectopic endometrium in the groin: (1) Implantation (applicable only to those cases associated with an inguinal hernia or a patent canal of Nuck); (2) direct extension along the round ligament from a neighboring process within the pelvis; (3) origin from cell rests of Müllerian origin; (4) metaplasia of "multipotent" serosal epithelium; (5) metastasis by way of the blood or lymph channels. Many of the cases reported in the literature were associated with hernial

sacs, and in these the implantation theory of origin has been most forcibly championed. In others the process was thought to have reached the groin by direct extension along the round ligament.

The following case is of interest, especially from a standpoint of pathogenesis, since no hernial sac existed and no pelvic peritoneal endometriosis was found at operation:

Mrs. H., Caucasian, was first seen in January, 1940, at which time the following notation was made upon her Clinic record:

"Aged 38. Hypertension for years. One sister has hypertension and nephritis. One child 17 years old. Menses regular. Two therapeutic abortions in 1936 and 1937. Now wants children. Has lump in the right groin the size of a hen's egg, 17 years' duration. This varies in size and is painful at times. It is above Poupart's ligament, not reducible, soft to palpation and there is no impulse on coughing. B.P. 160/90. Pelvic examination negative. Heart normal. Diagnosis: Essential hypertension, and hydrocele of the canal of Nuck. Patient advised against pregnancy and operation urged for removal of the inguinal tumor."

The patient decided against operation and was not seen until eighteen months later, at which time she returned after having missed one menstrual period. Pelvic examination revealed the uterus slightly enlarged, the cervix soft and a hard, freely movable mass the size of a handball in the right adnexal region. The breasts were slightly enlarged and the Friedman test was positive. The inguinal tumor was larger and was causing more discomfort.

The past history of Mrs. H. was carefully investigated. She was now 39 years old, had one child, aged 18 years, and two therapeutic abortions had been performed when she was several weeks pregnant, one in 1936 and the other in 1937, because of essential hypertension and chronic interstitial nephritis. For several years her blood pressure had been high, usually over 170 systolic and 120 diastolic, and the urine always contained albumin and casts. One sister has hypertension and nearly died in eclamptic convulsions during her only pregnancy six years before.

A diagnosis of pregnancy complicated by essential hypertension and fibroids of the uterus was made and therapeutic abortion, followed by pelvic laparotomy and removal of the inguinal mass, was advised and consented to. These procedures were carried out under cyclopropane anesthesia, on July 8, 1941, at her seventh week of pregnancy.

The diagnosis of pregnancy was substantiated by the uterine scrapings. At laparotomy, multiple fibroids were found, one pedunculated, the size of a baseball, in the right adnexal region. Both tubes and ovaries were normal in appearance. A subtotal hysterectomy was performed and the appendix removed. After closing the abdomen, the cystic tumor in the right inguinal region was dissected out and removed intact. It was not associated with a hernial sac. The patient's postoperative course was uneventful and she left the hospital in good condition. Follow-up examination six weeks after the operation showed her to be symptom free and in good health aside from the pre-existing hypertension.

Pathologic Examination.—The uterus revealed a large tumor mass, 5 cm. in diameter, arising from the right side of the fundus by a narrow

pedicle. Upon sectioning this presented the characteristic firm, white, whorled appearance of fibromyoma. Two smaller subserous myomas were present and the uterine wall contained many more. The appendix measured 6 cm. in length and no gross abnormality was noticed other than congestion of the serosal vessels.

The inguinal tumor was oval in shape and measured 6 by 4 by 3 cm. The external surface was smooth and bluish white in color. Upon opening, a single thin-walled cyst was disclosed, filled with serosanguineous fluid and lined by a smooth, shining fibrous membrane. At one pole an irregular mass of fat was present which was partially incorporated within the wall.

Microscopic examination of the uterine curettings revealed masses of decidual cells and chorionic villi covered by both syncytial and Langhans' cells, the normal histologic appearance of placental tissue in the

Fig. 1.—Photomicrograph showing decidual reaction in the wall of the appendix. ×260.

first trimester. Deep within the wall of the uterus were several islands of endometrium, consisting of glands surrounded by the usual stroma. Oddly enough, only a slight and certainly very patchy decidual reaction could be found in the stroma of the "adenomyomas" and several of them presented no sign of this change.

Two small cysts were present in the mesoappendix which were lined by flat epithelium and, just beneath the serosa, there were several small groups of decidual cells (Fig. 1). There was no histologic evidence of an inflammatory process.

Sections taken through the wall of the inguinal tumor revealed a striking picture. An epithelial lining was present which varied in nature from place to place. In some fields it was flattened, almost nonexistent, and in others it was tall columnar in type and invaginated, forming cryptlike spaces. Endometrium-like stroma, considerably distorted by hemorrhage, was present beneath the epithelium and scat-

tered here and there were sharply outlined nodules of unmistakable decidual cells (Figs. 2 and 3). The presence of large pigment-filled macrophages completed the picture, and there was no hesitation in classifying the tumor as an aberrant endometrial cyst.

The ectopic decidual reaction in the appendix and the presence of epithelial-lined cysts seemed to indicate that the latter, also, might be of endometrial origin, although the epithelium was not typical and no

Fig. 2.—Wall of the inguinal cyst showing a flat epithelial lining and nodules of sharply circumscribed decidual cells bulging into the lumen of a crypt. ×260.

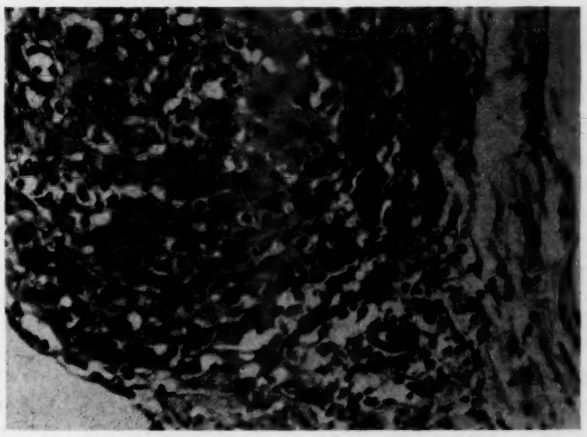

Fig. 3.—A mass of decidual cells in the wall of the inguinal tumor. ×580.

stroma, other than the decidual cells themselves, could be found. Novak[4] said, after reviewing a section of the appendix and the inguinal tumor: "The tumor of the inguinal canal shows what I think is undoubted endometrium in its wall. Such aberrant endometrium does not always show a typical stromal mantle, but the epithelium and the gland

invaginations are quite typical, and there are areas of stromal tissue including scattered patchy nodules of definite decidual cells. . . .

"The appendix likewise shows a number of small areas of decidual reaction, although there are no endometrial glands to be found. The two cystic spaces lined by very flat epithelium impress me as being peritoneal invaginations such as one not infrequently finds on many of the pelvic organs. It would hardly seem justifiable, on the basis of the section sent, to designate the appendiceal involvement as an endometriosis, especially in view of the fact that perfectly normal appendices are encountered which show a typical decidual reaction. Such cases are instances of the ectopic decidua which may be found, not only on the appendix, but on the back of the uterus, in the ovaries and elsewhere. They appear to indicate that vestigial patches persist in various parts of the pelvis which retain a sensitivity to the pregnancy hormone, but in view of the complete absence of epithelium and glands they can hardly be spoken of as areas of endometrium."

Pathologic Diagnosis.—(1) Pregnancy, first trimester; (2) multiple myomas of the uterus; (3) adenomyosis, uterus; (4) endometrial cyst of the groin; (5) ectopic decidual reaction, appendix; and (6) serosal inclusion cysts, appendix.

COMMENT

In considering the pathogenesis of the aberrant endometrium in this case, it is obvious that the lesion could not have resulted from direct implantation, since no communication existed between the peritoneal cavity and the groin; it is equally obvious that direct extension can be discarded as a source of origin since no sign of pelvic endometriosis was observed at operation. The endometrium, then, either must have reached the inguinal region through the blood or lymph channels or must have developed in situ by metaplasia of embryologically "multipotent" serosal epithelium.

There is considerable evidence at hand indicating that bits of endometrium may at times, although surely very rarely, gain access to blood or lymph vessels and produce distant lesions. Viable endometrium has been found in the pelvic lymph nodes on numerous occasions and cases of endometrium in the brachioradialis muscle and thigh have recently been reported (Navratil and Mankin). Hobbs and Bortnick[5] have succeeded in producing viable endometrial growths in the lungs of rabbits by injection of homologous endometrium, emulsified with normal saline, into the venous system. However, the generally sharp limitation of aberrant endometrial growths to the lower abdomen and contiguous structures indicates that the metastatic method of origin must apply only to exceptional cases.

In the present case it is suggested that the ectopic decidual reaction in the appendix, indicating an abnormal response to the hormones of pregnancy, is presumptive evidence that the full-fledged endometrial cyst of the inguinal region arose by metaplasia of bits of embryologically predisposed serosal epithelium, perhaps due to a different type of hormonal stimulation.

Normally, the endometrial stroma in the uterus responds to progesterone by a decidual reaction which becomes most marked just before menstruation. During pregnancy this change is tremendously accentu-

ated and the endometrium, at least the outer two-thirds, becomes converted into a mass of decidual cells. This hormonal "responsiveness," however, varies in different portions of the endometrium and generally decreases as the basal layer is approached. This feature is well illustrated in sections taken through the walls of pregnant uteri; the extreme basal portion of the endometrium takes little part in the formation of decidua.

A decidual reaction also occurs, under the influence of pregnancy, in the stroma of endometrial growths remote from the uterus, and it is likewise often "patchy" in nature. One of us (I. L. T.) has recently observed a case of widespread pelvic endometriosis at cesarean section in which the redundant hemorrhagic growths on the uterus, tubes, and ovaries clinically simulated an infiltrating malignant neoplasm; the question was settled by microscopic examination which revealed an extreme decidual reaction, masses of sharply outlined decidual cells compressing and surrounding relatively few dilated endometrial glands.

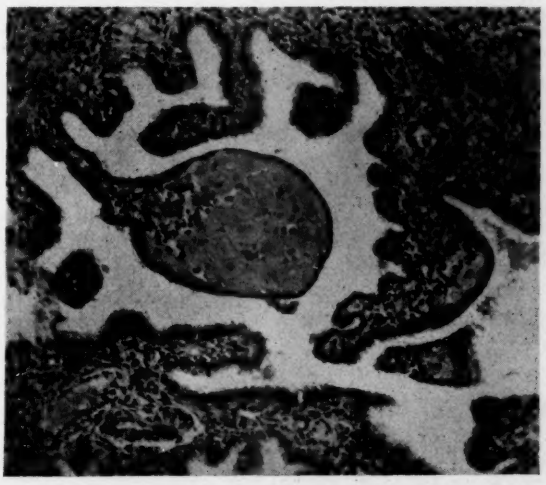

Fig. 4.—A group of decidual cells in the tip of a mucosal fold of a tube removed at a post-partum sterilization. ×260.

In this particular case the stroma cells of the ectopic endometrial growths were unusually sensitive to the pregnancy hormones. In other cases of endometriosis, this sensitivity, as evidenced by the formation of a decidual reaction, varies greatly from place to place, or may be missing entirely. In the case reported here, only a slight decidual reaction could be found in the stroma of the aberrant endometrium within the wall of the uterus, while a marked, although "patchy," reaction was present in the wall of the inguinal tumor.

Ectopic decidual reactions may occur alone in the complete absence of endometrial glands; we have seen a number in the walls and mucosal folds of tubes removed at post-partum sterilizations. One case presented a mass of sharply outlined decidual cells in the tip of a mucosal fold (Fig. 4) and careful microscopic search of the entire segment of tube removed at the operation failed to disclose endometrial glands. That such ectopic decidual reactions are not uncommon is conceded by may pathologists; yet there has been little mention of the condition in the

literature. One of the few cases reported is that of Reis and Sinykin[6] who described the occurrence of ectopic decidua in an appendix removed from a woman four months pregnant.

In view of the fact that bits of tissue remote from the endometrium have the ability to react in this manner to the hormonal stimulation of pregnancy, an intrinsic property of endometrial stroma itself, it is certainly reasonable to assume that such bits of tissue may, under a different type of hormonal stimulation, produce full-fledged endometriomas. The simultaneous occurrence of an ectopic decidual reaction in the appendix and an endometrial cyst of the groin in the present case lends support to this suggestion.

Witherspoon[7] has pointed out the frequent association of hyperplasia of the endometrium, myomas of the uterus and endometriosis and has advanced the hypothesis that all of these states are ultimately due to the same factor, the estrogenic principle from the ovary. This hypothesis is supported by a large amount of clinical and pathologic data, explains the frequent simultaneous development of the three conditions, and does not necessarily invalidate the implantation theory since some factor must determine and regulate the successful implantation and subsequent development of these hormone-labile bits of tissue.

SUMMARY

A case of endometrial cyst of the groin associated with a decidual reaction in the appendix is presented. The pathogenesis of the lesion is considered, and it is suggested that the aberrant endometrium in the groin arose by metaplasia of "multipotent" serosal epithelium. The absence of a hernial sac and associated pelvic peritoneal endometriosis, and the simultaneous occurrence of ectopic decidua in the appendix lend support to this suggestion.

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The author defines efficient reproduction as making each pregnancy count with resulting normal infants with the potentialities of normal adult life, at the same time with least maternal morbidity or mortality. The grande multipara does not do a very efficient job according to recent studies (Eastman, Yerushalmy and Kramer). National health demands spacing of pregnancies and forbearance on the part of the ill, dysgenic, and grande multipara. A woman should have her first baby after twenty and before twenty-five, and should end her childbearing career at 35.

R. J. Weissman.

BILATERAL DRY GANGRENE OF BOTH LOWER EXTREMITIES DUE TO ERGOT

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IT HAS been found from a review of the literature that peripheral gangrene is a rare complication of ergot administration. The following case is presented to emphasize the fact that serious complications from ergot do occur. Patients receiving the drug should be observed carefully for toxic manifestations and should not be given the drug indiscriminately.

CASE REPORT

Mrs. H. G., white female, aged 42 years, gravida viii, para v, was admitted to Grady Hospital on Jan. 12, 1942. Her chief complaint was pain in the lower abdomen, passage of large clots of blood from uterus, and pain in both legs.

The patient stated that her last normal menstrual period was on July 20, 1941. She was apparently having a normal gestation until Jan. 7, 1942. At this time without apparent reason she began to have cramplike pains in her lower abdomen, which were associated with uterine hemorrhage. A private physician was called and later the same night she passed a four and one-half months' fetus. The doctor administered fluid extract of ergot and told her to take one-half teaspoonful every four hours. On the following morning she began to complain of some tingling sensation throughout both lower extremities. She continued to bleed and have cramplike pains throughout that day and again called her physician. He applied hot packs to the extremities and advised her to continue taking one-half teaspoonful of fluid extract of ergot every four hours. She continued to bleed for two days and was seen again by her physician and told to continue the treatment. She bled for two more days and the cramplike pains throughout her abdomen were still present. On the fourth night she became irrational after having two chills followed by high fever. She was brought to the emergency clinic on Jan. 12, 1942. The total intake of ergot at home was two fluid ounces.

The patient had had 7 confinements and was always attended by a midwife, never receiving medication for post-partum bleeding.

On the day of admission, Jan. 12, 1942, the patient was apparently in shock, having lost a considerable amount of blood; pulse was 128, blood pressure, 70/?; and temperature, 101° F. The abdomen was essentially negative and was not tender. Examination revealed the cervix to be soft and about 3 cm. dilated. A piece of placental tissue about 5 cm. long was in the external os and was removed with a sponge forceps. Adnexa were essentially negative.

The anterior aspects of both lower extremities were extremely purple with discoloration which resembled erythema ab igne. Both dorsalis pedis and posterior tibial pulsations were present and the legs and feet were warm. There was marked muscle tenderness along the course of

the perineal nerves of both legs. There was no edema. The patient complained of exquisite tenderness in both lower extremities.

The tendon reflexes of both upper extremities were hypoactive, but equal. In the lower extremities all reflexes were absent. There was no muscular wasting and no fibrillary twitching.

Red blood cell count was 3,000,000, and hemoglobin 50 per cent. The patient was given a transfusion of 450 c.c. of whole blood. She was given one ampoule of ergometrine and 6 tablets of ergotrate gr. $\frac{1}{320}$ in a period of twenty-four hours. On admission she was given 2 Gm. of sulfathiazole and 1 Gm. every four hours; also 50 mg. of thiamine chloride and 50 mg. of nicotinic acid daily.

On the following day, January 13, temperature was 100.6° F.; pulse, 106; and she was irrational. The red cell count was 3,350,000; white cell count, 7,800; and hemoglobin, 56 per cent. An additional transfusion of

Fig. 1.—Lower extremities of the patient on the fifth hospital day.

400 c.c. was given, which was followed by a chill and elevation of temperature to 106.6° F., which dropped to 100° twelve hours later. The discoloration of the lower extremities was increased in intensity and the patient complained of inability to move her legs. Dorsalis pedis pulsations could be felt. Sedimentation rate was 125 mm. in one hour; bleeding time, eight minutes; and platelet count, 205,000.

On January 14, temperature was 100° F., and pulse, 110. The patient was not quite as irrational and her general condition seemed improved. There seemed to be a coalescing of the discolored areas which extended to the middle of both legs. The feet felt cold and dorsalis pedis pulsations were not felt, while those of the posterior tibials were questionable. The legs were elevated and hot water bottles applied.

On January 15, temperature was 100.6° F., and pulse, 120. The patient seemed rational and responded to questions intelligently. Lochia

was slight, and there was no tenderness in the course of the femoral veins. The legs now presented a typical picture of dry gangrene. Posterior tibials and dorsalis pedis pulsations were absent, and there was beginning demarcation in the middle third of the leg. Kahn report at this time was negative. A light tent was ordered and surgical consultation requested. That night a bilateral sympathetic bloc using 1 per cent novocain was done. No improvement was noted.

On January 16, the temperature was 99.8° F. and pulse 90. The patient seemed generally better. The toes at this time were mummified and the feet were plantar flexed. The femoral pulsations as well as the popliteals were good. Sulfathiazole was reduced to 1 Gm. every six hours. Blood cultures during all this time were negative.

On January 17, the patient was given 500 c.c. of blood and transferred to the surgical service.

Fig. 2.—Section through a blood vessel showing premortem clot and changes in the intima (×30).

Temperature and pulse remained normal, and on January 21 the line of demarcation had become well established at the middle of the upper third of the leg. The left leg was amputated under sodium pentothal anesthesia. The patient stood the operation well and was given 250 c.c. of plasma postoperatively and 250 c.c. of whole blood the following day. Postoperative course was uneventful.

Four days later, January 25, the right leg was amputated, the patient having received several preoperative transfusions of whole blood and plasma.

Remainder of the postoperative course was uneventful and the patient was dismissed from the hospital on February 5, her twenty-fifth hospital day.

PATHOLOGIC FINDINGS

The upper half of the leg was normal in appearance. At the midportion of the leg there was an irregular line of transition from a normal appearance to a bluish gray discoloration. This discoloration continued down over the dorsum and sides and posterior portion of the foot, until it reached about 1 cm. proximal to the roots of the toes, and 1 cm. superior to the sole of the foot. Another line of demarcation which was fairly sharp was at a point where the skin and underlying soft tissues had been much shrunken, and had the appearance of mummification. As the foot was held up to the light these mummified parts were translucent. The skin and subcutaneous tissues underlying the grayish blue discoloration were very edematous and had a slightly hemorrhagic appearance.

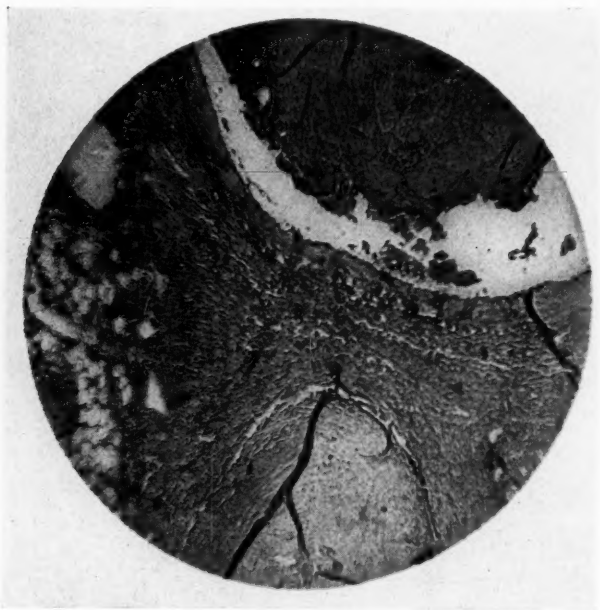

Fig. 3.—Section through a vessel and nerve showing premortem clot, intimal changes and toxic changes in the nerve bundles (×30).

As the gastrocnemius muscle was dissected, scattered areas of extravasated blood were noted. As the vessels and nerves of the leg were dissected there were noted in the arteries fairly firm thrombi which had the appearance of being premortem. Otherwise there was no recognizable gross pathology of the vessels and nerves.

A section through the skin and subcutaneous tissue taken from the lower third of the right leg revealed hyperkeratoses of the epidermis and necroses of the epithelial cells. The corium was markedly edematous and fragmented. In the subcutaneous tissue there was a vessel, apparently a vein, whose wall was markedly edematous and fragmented, and whose lumen contained a post-mortem clot. A section through the muscle tissues of the leg revealed the sarcolemma to have completely disappeared in some areas. In others it was present but was rather widely separated from the muscle fibers. The muscle fibers had lost

their nuclei, but the striations were quite definite. Between the muscle fibers, there was a sparse infiltration of polymorphonuclear neutrophiles. Another section was through nerves, arteries, and veins. The arteries showed what was apparently some medial thickening and slight reduplication of the internal elastic lamina. Many of the veins contained premortem thrombi, some of which showed very early organization. The walls of the veins were infiltrated with small round cells and plasma cells, particularly the outer part of the media and adventitia. There was some fibroblastic activity in the media. Most of the nerve bundles showed marked degeneration. The connective tissue binding the arteries, nerves, and veins together showed a rather marked fibroblastic reaction, was very vascular, and was densely infiltrated with small round cells, plasma cells, and a few polymorphonuclear neutrophiles. A section taken at the junction of the mummified skin of the foot and the adjacent skin revealed both surfaces to be covered with hyperkeratotic degenerating stratified squamous epithelium. In the underlying corium, however, there was a sharp line of demarcation between the two areas. The corium of the mummified part was dense, acellular, and hyaline, while the adjacent tissue was edematous and fragmented.

COMMENT

The toxic manifestations of ergot may take two different forms: One affects the central nervous system and is characterized by headache, vertigo, nausea, and frequently convulsive seizures, thirst, and confusion. This may be followed by depression and syncope, which may cause death. The other form is characterized by lowering of blood pressure, parathesias, anesthesias, muscular pains, and cyanoses of the extremities, particularly the digits. The latter may rapidly assume the dry form of gangrene.

The pathogenesis of gangrene in ergot intoxication has been demonstrated to be a primary vascular spasm followed by thrombosis due to stasis and injury to the intima. The pathologic picture of ergot gangrene is usually one that shows marked proliferation of the intima, thrombus formation in the vessels, thrombophlebitis and ischemic changes in the nerves.

Toxic effects usually follow the administration of the drug over a long period of time. There is evidence that some patients may have an idiosyncrasy to the drug, as shown by a report where one drachm of the fluid extract caused symptoms. Gangrene and death have occurred after taking 12 gr. of the extract.

While it is possible that this woman had an idiosyncrasy to the drug, her condition was unquestionably due to overdosage.

It is to be remembered that the patient first complained of tingling in the lower extremities following the administration of the fourth dose of one-half drachm of the fluid extract. However, it must also be remembered that over a relatively short period of time she received two ounces of the fluid extract equivalent to 960 gr. plus six 1/320 gr. tablets of ergotrate plus 1 ampoule of ergometrine. This is well over the toxic dose. Therefore it is gathered from the above facts that a large dose of the drug with the possibility of a slight sensitivity resulted in marked vascular disturbance of the lower extremities. This in time caused a complete bilateral symmetrical dry gangrene.

From the history of this case and the pathologic findings which were presented it is assumed that this is one of ergot gangrene.

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BILATERAL OVARIAN CARCINOMA ASSOCIATED WITH INTRAUTERINE PREGNANCY

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OVARIAN neoplasms associated with pregnancy occur infrequently. The incidence usually quoted is 0.1 per cent or less. There are only a few reports of malignant new growths combined with pregnancy. In those which have been reviewed, malignant disease was found in from 5 to 7 per cent of the pregnancies complicated by ovarian tumors.

We were able to collect a total of 14 cases, including the present report, of malignant ovarian disease with pregnancy. Szathmáry, in 1933, reported 3 cases of his own which are included in our group. This author, also, brought out the fact that he had found 39 additional cases in the literature. Of the 39, 7 had sarcomas and the rest carcinomas. These cases were not described in any detail. In our group, 5 had sarcomas and the remainder carcinomas. The case of Hempel which was reviewed could well have been a Krukenberg type of new growth because there were bilateral ovarian tumors which were secondary to a carcinoma of the stomach. There may well be some question as to the diagnosis of sarcoma which was made in certain of the cases, if one considered the present-day concept of the pathology of the ovarian neoplasms. Table I briefly outlines the cases which we found in the literature.

The cases of Kosmak and Traut and Kuder are the only ones that were found in the American literature. Therefore, we regard it to be of sufficient rarity and interest to report ours.

T. B., a 42-year-old, white married woman, was admitted to the Cincinnati General Hospital, No. 165203, for the first time, Oct. 28, 1941. Six months prior to her admission, the patient had been aware of a gradual increase in the size of the lower abdomen along with a dull, aching pain in the right lower portion most of the time. Upon arising, Oct. 26, 1941, the pain suddenly became severe and cramp-like. It continued so until the morning of the date of hospitalization, at which time it became most intense. There was neither nausea nor vomiting. The appetite had been poor since the onset of the acute pain. The last bowel

TABLE I. SUMMARY OF REPORTED CASES

AUTHOR	TYPE OF TUMOR	PERIOD OF PREGNANCY TUMOR WAS FOUND	TREATMENT OF TUMOR	TERMINATION OF PREGNANCY	RESULT
Swan in 1897 quoted the following 3 authors and their cases:					
Spiegelberg (1867)	Myxosarcoma, bilateral	Post partum	None	Spontaneous delivery	Died ninth day
Hempel (1875)	Carcinoma, bilateral and secondary to gastric carcinoma	Post partum	None	Spontaneous delivery	Died twenty-eighth day
Ruge (1886)	Myxosarcoma, bilateral	Sixth month	No further details given		
Zickel (1907)	Adenocarcinoma, unilateral	Seventh to eighth month	Removed	Spontaneous delivery eighth day	Died 3 months; carcinomatosis
Kosmak (1914)	Adenocarcinoma, unilateral	"Early"	Removed	Aborted on fourth day	Well
Szathmáry (1933)	Small round cell carcinoma, unilateral	4½ months	Removed	Spontaneous delivery	Well
	Round cell carcinoma, unilateral with extensive pelvic tuberculosis	Post partum, first day	Complete removal	Spontaneous delivery	Well
	Spindle cell sarcoma, unilateral	2½ months	Removed	Spontaneous delivery at term	Well
Trillat and Puthod (1934)	Atypical epithelial carcinoma, unilateral	Term	Removed at time of section	Cesarean section	Not mentioned
	Lymphosarcoma, unilateral	"Early"	No further details were given		
	Papillary cyst Adenocarcinoma	Post partum, eleventh day	Removed	Spontaneous delivery	Died
Traut and Kuder (1940)	Papillary cyst, adenocarcinoma	No details were given			
	Adenocarcinoma	Fourth month	Complete removal	Removed at operation	Well
Bossert* (1942)	Papillary serous cyst adenocarcinoma, bilateral	Second to third month	Complete removal and deep x-ray therapy	Removed at operation	Well after 3 months

*Case reported in the present paper.

movement occurred following an enema two days before admission. There were no urinary tract symptoms.

Menstruation began at the age of 13 years, recurring regularly every twenty-eight to thirty days. The periods were usually of three days' duration, but in recent years nine days. The flow was never heavy. A slight vaginal discharge was present for several months. The last period occurred Aug. 29, 1941, and the previous menstrual period was Aug. 1, 1941.

The patient had been married twenty-three years. There had been 6 full-term uncomplicated deliveries and 2 miscarriages. The last term pregnancy occurred twelve years ago. All of the children were well. Her past health had been good until two years ago. During this time there were intermittent aching pain in the right lower abdomen and throbbing headaches in the right frontal and occasionally, in the right temporal areas, dizziness and some blurring of vision.

On physical examination, the temperature was 97° F., the pulse rate 92 per minute, the respiratory rate 20 per minute, and the blood pressure 175 systolic over 110 diastolic. She appeared moderately acutely ill. There was slight dehydration. The color was good. The head and neck were normal except that the upper teeth were absent, the lower ones were carious, and the thyroid contained a small nodule. The lungs and heart were normal. The breasts were negative and no enlarged lymph glands were palpable.

The abdomen was rounded, extended slightly above the level of the costal margin, and moved with respirations. The right lower quadrant was more prominent than the remainder of the abdomen. The liver and spleen were not felt. A definite cystic, tender mass which extended to the umbilicus was lying in the right lower quadrant. A questionable smaller mass was found in the left lower quadrant. There was no costovertebral angle tenderness. Peristalsis was good.

Vaginal examination revealed normal external genitals. The urethra was healthy. There was no infection of Skene's or Bartholin's glands. The perineum was lacerated and a moderate sized rectocele was present. The anterior vaginal wall was slightly relaxed. Although the vaginal mucosa appeared healthy, a moderate amount of greenish yellow, somewhat foamy discharge existed in the vagina. The cervix was soft and its surface was rough as a result of several small lacerations. The uterus was difficult to outline, but it was felt to be anterior and to the left. The size was normal. A large, cystic tender mass arose from the right appendages and extended into the abdomen as described. A smaller cystic nontender mass involved the left ovary. Rectal examination was negative. The remainder of the examination was not unusual.

Our impression was that the patient had bilateral ovarian cysts with probable torsion of the pedicle or intracapsular hemorrhage of the right tumor.

The laboratory findings were as follows: The urine was negative; hemoglobin, 14 Gm.; white blood cell count, 9,050; and Wassermann reaction, negative.

The following notation was made by Dr. V. Bradley Roberts at the time of the pelvic examination under ether anesthesia, Oct. 29, 1941: "An intrauterine pregnancy is very likely. The larger of the two tumors is on the left side and the smaller one on the right."

The operative note as of the same date reads as follows: "Immediately upon opening the abdomen a large amount of blood-tinged

fluid without odor escaped. On the right side was a dark, semi-solid tumor about the size of an adult fist, one surface of which was adherent in the pelvis. The tumor had a strangulated appearance. On the left side was a ruptured large cyst approximately the size of an adult head. The uterus was soft and enlarged to about the size of a ten weeks' pregnancy. Metastatic implants were present on the left broad ligament as well as on the bladder peritoneum. There were no mesenteric nodes, no nodules in the peritoneum, and no metastatic involvement of the liver."

Supravaginal hysterectomy and bilateral salpingo-oophorocystectomy were done. The small implants were removed with the specimen.

The patient withstood the operation well. Her course was afebrile and the wound healed by primary union. The patient complained that the throbbing headache noted in the past history was more intense. A thorough neurologic investigation revealed no definite cause for this complaint. Roentgenograms of the skull, chest, and pelvis showed no metastatic involvement. Deep x-ray therapy was started on the seventeenth postoperative day and the patient was discharged on the twenty-first day.

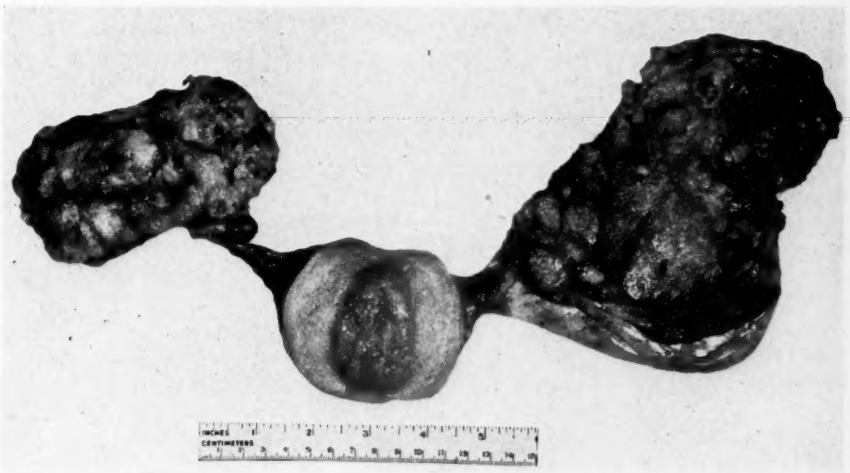

Fig. 1.—Sagittal section of the uterus and the tumors.

After three months, the patient has remained well. During this period of time 13,000 r. units of deep x-ray therapy through 6 portals have been given.

The pathologic description of the specimen is as follows:

Gross.—The specimen consisted of the uterus, tubes, and ovarian tumors (Fig. 1). The dark red and softened uterus was symmetrically enlarged to twice its normal size. Anterior median section revealed a pregnancy. The placenta was implanted on the posterior wall. Upon opening the amniotic sac, a 2.5 cm. fetus was recovered. The tubes were normal in all respects. The left ovary was replaced by a ruptured cyst, 20 cm. in diameter. The outer surface was glistening and grayish white in color. It was smooth except for one discrete, small, firm papillary projection. The inner surface was completely studded with fused papillary excrescences which were deep red, rough, and firm. The right

ovary was involved in a soft semisolid tumor which measured 12 by 6 by 4 cm. The surface was smooth except for one small, slightly elevated, firm, yellow area. The content was brainlike in character and had the same dark color as the surface.

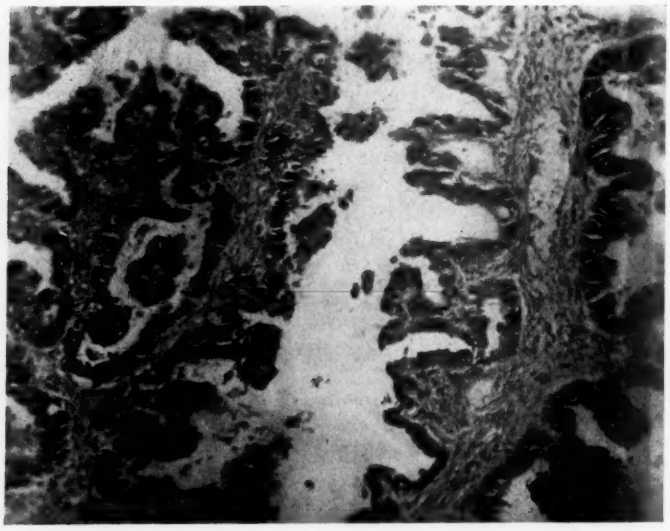

Fig. 2.—Microphotograph of the left ovarian tumor.

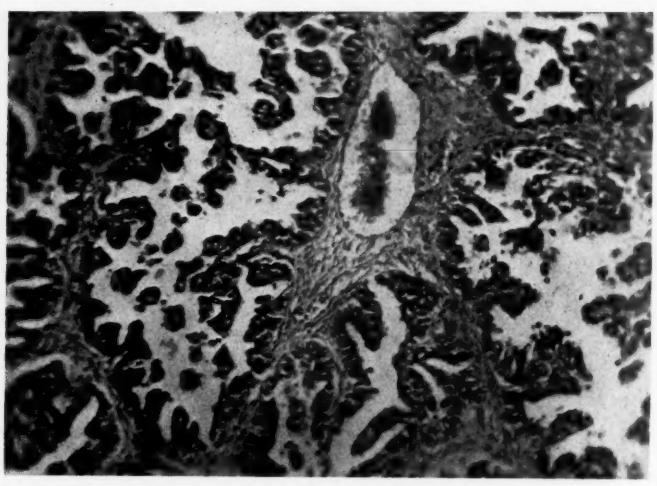

Fig. 3.—Microphotograph of the right ovarian tumor.

Microscopic.—The left tumor (Fig. 2) was predominantly papillary. The capsule was composed of dense fibrous tissue. Its thickness was decreased in some places due to the encroachment of the epithelial elements of the tumor. The connective tissue stroma was scant in amount. The papillas were lined by 2 to 3 layers of epithelial cells. The latter were both polygonal and columnar in form. The taller cells were greater in number. The nuclei were large and almost filled the entire cell. They

were hyperchromatic and showed numerous mitotic figures. Nucleoli were occasionally seen. The solid tumor (Fig. 3) was adenomatous and papillary in character. Gland formation was not very distinct. The fibrous tissue capsule was less than 0.5 mm. in thickness. Again, the stroma was scant and delicate. The individual cells were similar to those of the other tumor. In both tumors proliferation and infiltration were evident and there were large areas of necrosis. The solid tumor appeared to have a greater degree of malignancy than the left. The corpus luteum of pregnancy was never satisfactorily demonstrated.

The pathologic diagnosis was serous papillary and adenocarcinoma of the ovaries associated with an early pregnancy in the uterus.

DISCUSSION

Laparotomy is indicated when a proliferating type of ovarian tumor 8 cm. or more in diameter is found in the pregnant woman, because the question of malignancy can never be completely made without it in the majority of cases. If a definite diagnosis of ovarian malignancy is made prior to operation, the indication for the laparotomy should be based upon the extent of the lesion. In the inoperable case, the pregnancy could probably be permitted to go to term. Contrarily, however, in the operable case immediate operation is strongly recommended with no regard to the period of gestation.

Several factors determine the advisability of the removal of the pregnant uterus. The findings at the time of the operation are most important. A distinction should be made between young and old patients, primiparas and multiparas. For example, a complete operation would more likely be done in the woman approaching 40 years of age, who has one or more healthy children than in the younger woman, who is pregnant for the first time.

CONCLUSIONS

There are two points which should be emphasized in conclusion:

1. Careful prenatal examination is necessary for the early diagnosis of ovarian tumors in the pregnant woman.
2. Where possible, the nature of the tumor should be well known at the time of laparotomy in order to carry out the proper procedure.

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UNILATERAL TWIN ECTOPIC PREGNANCY

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UNILATERAL tubal twin pregnancy is of sufficiently rare occurrence to justify this report.

In 1923 Arey, reviewing all reported cases of twin unilateral ectopic pregnancy, found 38 authentic or positive cases and added 2 of his own. He also found and classified 8 as probable or presumptive and 4 as possible but doubtful cases. Falk and Blinick in 1938 found 23 additional positive cases published since the work of Arey and added 2 cases of their own to make a total of 65 authentic reported cases. Christitch added another case. Fishback in 1939 reported a case of simultaneous twin pregnancy in one tube and a single pregnancy in the other tube. Also in 1939 Kaplan reported 2 cases of twin ectopic pregnancy; Reček, of Czechoslovakia, reported a case and recently Fischmann reported a case of interstitial twin pregnancy. To the accepted list of 71 authentic cases, we are reporting an additional one. It might be added, that to our knowledge, this is the first case of its kind at the Cook County Hospital, there having been a total of 903 ectopic pregnancies in the last sixteen years, as far back as we were able to investigate.

M. D., a 30-year-old, colored female, grav. i, para o (having had a spontaneous abortion in 1940), who was separated from her husband eight years previously, entered on the senior author's gynecologic service of the Cook County Hospital, May 20, 1941, with the complaints of abdominal cramps and nausea and vomiting for three weeks. The patient stated that she was perfectly well until three weeks ago, when, after eating breakfast, she became nauseated, vomited, and then experienced "cramps" in the lower abdomen, which were eased by the application of a hot water bag. This syndrome of eating followed by nausea and vomiting with subsequent abdominal cramps and soreness had continued almost daily for three weeks. Her last normal menstrual period occurred March 19, 1941, at which time she flowed for three days, moderate in amount, passed no clots, and had her usual mild abdominal cramps on the first day. The past 2 menstrual periods, which occurred April 19 and May 18, 1941, were characterized by cramping pains in the lower abdomen after spotting for one day on both occasions. Prior to April her menstrual periods had been of the twenty-eight-day type. Three days ago while working she experienced severe pains in the suprapubic area. These lasted about two hours and then subsided upon lying down. The following day on arising from bed she again experienced abdominal pains, this time lasting approximately two and one-half hours. The abdominal pains were described as dull, cramping in character, only at times being sharp and knifelike, which would subside on lying down. The pains usually were in the right lower quadrant and radiated at times to the left lower quadrant. There was no history of fainting.

Physical examination revealed a fairly well-developed, colored female, who appeared to be acutely ill. Temperature was 99.4° F.; pulse, 108;

respiration, 20; blood pressure, 120/80. The head, neck, heart, and lungs were not pathologic. The breasts were slightly enlarged, the nipples were tender, and a straw-colored secretion was expressed from both nipples. The abdomen was round, firm and elastic. There was definite tenderness in the lower abdomen, more marked in the right lower quadrant, rebound tenderness, and a voluntary muscular rigidity. No mass was palpable nor were the kidneys, liver, or spleen. Pelvic examination revealed a nulliparous introitus, a slight mucopurulent discharge was expressed from the urethra and Skene's ducts, and there were bilateral shotty Bartholin glands. The introitus admitted 2 fingers and the pelvic floor was firm and elastic. The posterior vaginal wall

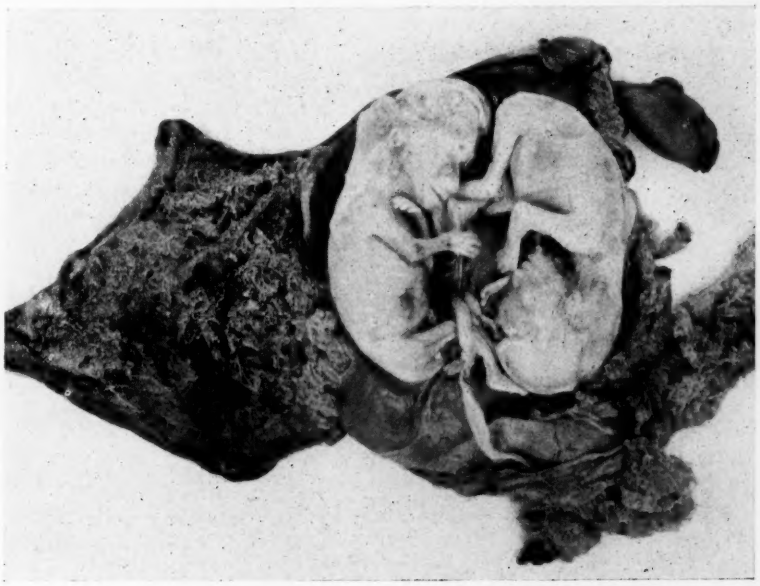

Fig. 1.

appeared to be raised by a bulging, doughy, tender mass in the cul-de-sac of Douglas. The cervix was soft and smooth, and the os was patulous and pointed down and backward. Attempt at movement of the cervix elicited pain in the lower abdomen, especially in the right lower quadrant. The corpus was not definitely made out due to the extreme tenderness present; however, it was thought to be slightly enlarged, softened, smooth, and pushed toward the left by a tender cystic mass about the size of an orange in the right adnexal area. The left adnexa were tender, but no definite structures were made out. Rectovaginal-abdominal examination confirmed the above, and speculum examination revealed a smooth cervix which took the Schiller stain well. The Falls-Freda skin pregnancy test gave no reaction after thirty and sixty minutes. The hemoglobin was 75 per cent (Tallqvist); red blood count, 3,820,000; white blood count, 9,200; Kahn test, positive; urine, essentially negative. A diagnosis was made of an old-ruptured right ectopic pregnancy with hematocele.

The following day, under nitrous oxide and ether anesthesia, the patient was subjected to a laparotomy. On opening the abdomen, the

peritoneum was congested and purplish, and when the latter was incised, there was a slight amount of fresh and old-clotted blood in the peritoneal cavity. The uterus was enlarged to the size of approximately a six to eight weeks' gestation, was soft, hyperemic, and pushed to the left by the right tube which was enlarged and deformed by a soft cystic mass about the size of an orange. The tube was ruptured in the ampullary portion, but the sac was intact. In attempting to deliver the sac, the latter ruptured and two fetuses about the size of an eight weeks' pregnancy were revealed. Since the right ovary was not pathologic, a right salpingectomy was done. Exploration of the left tube and ovary revealed no pathologic findings, and the abdomen was closed. The patient made an uneventful recovery, being discharged from the hospital on the tenth postoperative day.

The following is the pathologic report submitted by Dr. A. B. Ragins of the Department of Surgical Pathology: "Specimen (Fig. 1) consists of a Fallopian tube previously opened and measures 14 cm. in length and 6 cm. in greatest circumference. The external surface is light purplish gray and covered by clotted blood. In the lumen of the tube wall, which is thickened, is a soft papillary structure, resembling placental tissue and 2 fetuses measuring 5.5 cm. (crown-rump). On tracing the umbilical cords to the placenta 2 amniotic cavities were demonstrated, separated by a thin membrane. Gross diagnosis: twin pregnancy of a Fallopian tube. Microscopic: Section of wall of Fallopian tube reveals placental tissue."

SUMMARY

We are adding another case of unilateral twin ectopic pregnancy, making a total of 72 reported cases. During the preparation of this report, Dr. F. H. Falls, of the Department of Obstetrics and Gynecology, University of Illinois, notified us by personal communication that he also has a gross specimen of an ectopic twin pregnancy in the ampullary portion of the tube, as yet unpublished.

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A SIMPLIFIED METHOD OF GLYCOGEN ESTIMATION IN UTERINE MUCOSA FOR CLINICAL PURPOSES

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IN THE cyclic development of the uterine mucosa, two phases are distinguishable: (a) the proliferative phase, brought about by the activity of the follicular hormone and (b) the progestational phase, brought about by the activity of the corpus luteum hormone. In the second phase, anatomic as well as functional changes can be detected: The glands become dilated and coiled and produce mucus and glycogen. Glycogen determinations have been carried out mainly by histochemical methods using Best's glycogen staining. Quantitative glycogen estimations in uterine mucosa have been carried out by van Dyke and Chen[1] in monkeys. Zondek and Stein[2] published quantitative estimations of glycogen with Pflueger's method in human curettage material. They obtained the following results: During the first generative phase (the proliferative phase) human uterine mucosa contained about 0.1 per cent of glycogen in fresh tissue. During the progestational phase the glycogen content rose, the minimum being 0.25 per cent, the maximum 0.66 per cent. In 18.4 per cent of 49 cases of sterility examined, glycogen content in the second phase was much below this minimum of 0.25 per cent although all anatomic changes of the uterine mucosa were normal. This condition of glycogen deficiency has been termed "glycopenia uteri." It was assumed that insufficient glycogen quantities in the uterine mucosa interfere with the imbedding of the fertilized ovum.

Estimation of glycogen in the uterine mucosa of the second generative phase may, thus, serve to determine the cause of sterility, especially in patients with normal menstruation. The purpose of the present paper is to describe a simple method for glycogen estimation suitable for routine tests and not requiring the collaboration of a chemical laboratory. The method elaborated does not yield exact values but is sufficient, from a clinical point of view, to determine whether glycogen is produced in sufficient amounts in the endometrium or not.

Glycogen is generally estimated in laboratories by Pflueger's method: Digestion of the tissue with concentrated potassium-hydroxide, precipitation of the glycogen with alcohol, hydrolysis of the washed glycogen precipitate and sugar estimation in the hydrolyzate. In our method we tried to avoid the last two manipulations, i.e., hydrolysis and sugar estimation. This was done by means of the color reaction of glycogen with iodine.

EXPERIMENTAL

As no sufficient quantities of uterine mucosa were available, the glycogen-iodine reaction was standardized with crude liver glycogen (purified glycogen was found to be unsuitable).

Crude liver glycogen was prepared by digestion of fresh liver in 60 per cent KOH dilution with 2 volumes of water and precipitation of the glycogen with 4.5 volumes of 96 per cent alcohol. The precipitated glycogen was washed with 70 per cent and 96 per cent alcohol, and a solution was prepared in water containing 1 mg./ml. glycogen (accord-

ing to Pflueger's glycogen estimation). From this standard solution various dilutions were prepared, and to 1 c.c. of each solution 3 drops of N/10 iodine solution in potassium iodide were added. The same quantity of iodine solution was added to 1 ml. of distilled water, and to this water-iodine solution drops of 20 per cent neutral iron chloride solution were added until the color became identical with that in the glycogen iodine solutions. The results shown in Table I were obtained.

TABLE I

Concentration of glycogen mg./ml.	1.0	0.5	0.4	0.3	0.25	0.2	0.1
Drops of iron chloride necessary to produce color equality	>15	>15	>15	5	3	2	1

From the above results it can be seen that in the narrow range from 0.25 mg./c.c. to 0.40 mg./c.c., the number of drops of iron chloride required to produce color equality rises from 3 to over 15. Advantage was taken of this fact in the following procedure for estimation of glycogen content in the uterine mucosa.

METHOD FOR ESTIMATION OF GLYCOGEN CONTENT IN THE UTERINE MUCOSA

One hundred and twenty-five milligrams of fresh uterine mucosa are digested in a centrifuge tube by adding 0.15 ml. 60 per cent KOH and heating for one hour in a boiling water bath. (If this cannot be done immediately, the mucosa must be kept on ice.) After boiling, 0.3 ml. water and 0.7 ml. 96 per cent alcohol are added and the tube dipped for a short time into the hot water bath. The tube is centrifuged and the supernatant discarded. The precipitate is washed, once with 70 per cent and once with 96 per cent alcohol. The washed precipitate is dissolved in 1 ml. water by warming in a water bath. With this solution the iodine color test was carried out.

Solutions required: (1) N/10 Iodine solution: 25 Gm. of potassium iodide are dissolved in a small quantity of water, 12.7 Gm. iodine are added and when all has dissolved water is added to 1 liter. (2) 20 per cent "neutral" ferric chloride solution: 20 Gm. ferric chloride are dissolved in 100 ml. water and drops of 2N NaOH are added until a permanent precipitate forms. After filtration the solution is ready for use and can be kept in a closed flask for one month.

Iodine Color Test.—Add to 1 ml. of the glycogen solution obtained by the above described procedure, 3 drops of the N/10 iodine solution and to a second test tube of the same size 1 ml. water and 3 drops of iodine. Now, add drops of the ferric chloride solution to the water-iodine test tube until color equal to the glycogen iodine is obtained.

Calculation.—According to the results obtained with liver glycogen, concentrations of less than 0.25 mg./ml. need less than 3 drops of ferric chloride for color equality. In our procedure, 1 ml. of the glycogen solution corresponds to 125 mg. uterine mucosa, i.e., 0.25 mg./ml. means 0.25 mg./125 mg. uterine mucosa or 0.2 per cent. When 0.3 mg./ml. or approximately 0.25 per cent of mucosa are present, 5 drops are needed and concentrations above 0.4 mg./ml. or 0.32 per cent of uterine mucosa require more than 15 drops. Hence, in order to convert the figures for glycogen concentration from mg./ml. (Table I) into figures of per cent glycogen in the uterine mucosa (Table II), they must be multiplied by 0.8.

This is summarized in Table II.

TABLE II

NUMBER OF DROPS OF FERRIC CHLORIDE REQUIRED	GLYCOGEN CONTENT OF MUCOSA UTERI
Less than 3 drops	Less than 0.20 per cent
3-5 drops	0.20-0.24 per cent
5-15 drops	0.24-0.32 per cent
More than 15 drops	More than 0.32 per cent

This technique of assay was now compared with the results obtained with Pflueger's method for glycogen estimation. The results shown in Table III were obtained.

TABLE III. GLYCOGEN CONTENT OF SAMPLES OF MUCOSA TAKEN FROM STERILE WOMEN

UTERINE MUCOSA NO.	DAY OF CYCLE	DROPS OF $FeCl_3$ REQUIRED	GLYCOGEN CONTENT ACCORDING TO OUR METHOD	PER CENT GLYCOGEN ACCORDING TO PFLUEGER'S METHOD
1	11	15	0.24-0.32%	0.26
2	11	15	0.24-0.32%	0.26
3	12	1	less than 0.2%	0.03
4	12	1	less than 0.2%	0.05
5	17	15	0.24-0.32%	0.3
6	18	1	less than 0.2%	0.08
7	20	15	0.24-0.32%	0.27
8	23	>15	more than 0.32%	0.64
9	23	0	no glycogen detectable	0.03
10	25	15	0.24-0.32%	0.28
11	25	2	less than 0.2%	0.08
12	25	>15	more than 0.32%	0.38
13	25	4	0.2-0.24%	0.21
14	26	8	0.24-0.32%	0.27
15	26	< 3	appr. 0.2%	0.18
16	26	>15	more than 0.32%	0.36
17	26	>15	more than 0.32%	0.40
18	27	>15	more than 0.32%	0.60
19	28	>15	more than 0.32%	0.37
20	28	>15	more than 0.32%	0.37

The table shows that information obtained by our simplified glycogen test is in good agreement with that obtained by Pflueger's method. In agreement with the results of Zondek and Stein,[2] 3 cases (Cases 6, 9, and 11) out of 16 cases (Cases 5-20) in the second phase showed glycogen deficiency.

SUMMARY

A simplified glycogen test for uterine mucosa is described. The test is based on the iodine glycogen color reaction, but does not require the use of a colorimeter. It is sufficiently accurate for detection of sufficiency or insufficiency of glycogen production in the uterine mucosa.

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A REVIEW OF THE CALDWELL-MOLOY METHOD OF ROENTGEN PELVIC MENSURATION WITH A CORRELATION OF NEW TECHNICAL PROCEDURES

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RECENTLY some minor technical changes have been applied to Caldwell and Moloy's method of depicting roentgenographically the osseus structures of the maternal pelvis.

The method described in the literature numerous times consists basically of:

(a) Stereoroentgenographic examination of the pelvic inlet
(b) Roentgenographic examination of the pelvic outlet
(c) Lateral roentgenographic examination of the maternal pelvis with centimeter measurement of the true conjugate

Roentgenographic examination of the maternal pelvis requires first of all accurate posturing of the patient with elimination of roentgenographic distortion in order that interpretation and typing of the pelvis may be made without undue difficulty.

Some means of adjusting the normal plane of the pelvic inlet to have it coincide with the plane of the film is essential for accurate interpretation. Caldwell and Moloy advocated the use of a lumbosacral pad to be placed under the curve of the lumbar spine to adjust, or tilt, the plane of the inlet so that it would be in the identical plane of the film, thereby eliminating distortion in the image. Recently I[3] described an angle block to meet the same requirements as the pad and pointed out some advantages in using the block. A description of this apparatus appears in the reference.

I[4] recently worked out something hitherto untried concerning roentgenography of the inferior pelvic aperture, or pelvic outlet. Working on the theory that stereoroentgenography is superior to single film roentgenography stereoscopic studies were carried out on the pelvic outlet. In this connection it may be pointed out that in orthopedic work stereoroentgenography of the inferior pelvic aperture reveals detail that might remain undisclosed by single film examination. The application of this projection to the pelvic outlet was thought of. In this connection an oblique anteroposterior projection for stereoroentgenography of the inferior pelvic aperture was initiated as follows: With the patient placed in a supine posture on the roentgenographic table, the superior border of the symphysis pubis is oriented on the Potter-Bucky diaphragm so that it coincides with the caudal edge of a 10 by 12 cassette, the short axis of which is in the median plane. The tube is angulated 45 degrees cephalad and the central ray is projected through the localization point (a point 5 cm. caudad to the superior border of the symphysis pubis, Fig. 1) to the film. The roentgen tube is shifted transversely for the stereoroentgenograms.

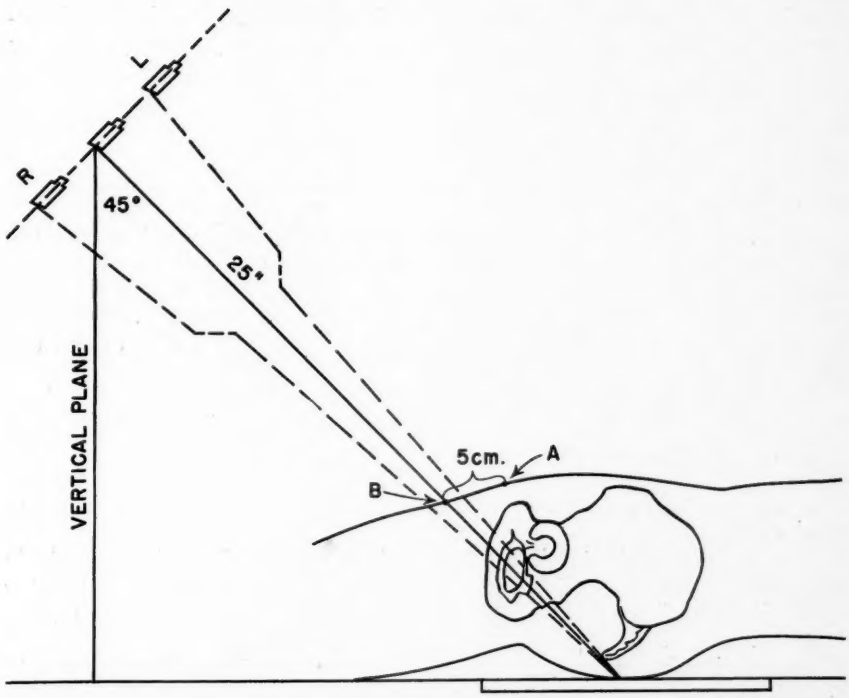

Fig. 1.—Diagram depicting direction of central x-ray beam for stereoroentgenography of the pelvic outlet.

Fig. 2.—Radiograph of pelvic outlet.

It is not believed that this technique has been described in the literature except in dealing with fractures of the inferior pelvic aperture by the author, and hence has not been universally adopted for roentgenographic examination of the pelvic outlet. No doubt added research will be required prior to evaluating its connection with the pelvic outlet and prior to its adoption by the obstetric and roentgenologic professions. There is the possibility, however, that it may enhance the evaluation of the Caldwell-Moloy method.

So far as concerns the initial description of lateral roentgenography of the maternal pelvis one change was recently made at the Margaret Hague Maternity Hospital[2] by adopting a thin rule of light weight for measurement of the true conjugate, on the roentgenogram. This has recently been described in the literature and attention is again drawn to the reference.

In explanation, the rule consists of a hollow bakelite stem with alternate strips of lead and bakelite, each measuring 1 cm. in length, inserted within the hollow stem. Its extremely light weight prevents its slipping away from its strapping and the centimeter margins are more readily seen on the roentgenogram than was the case with the older brass or steel rules.

It may be seen that minor changes in technique have been made in each of the three types of studies required to complete the Caldwell-Moloy method of pelvioroentgenography and no doubt has enhanced the value thereby.

Concerning stereoroentgenography of the plevic outlet it may be found out later on after more study that this too has added something to the most excellent method first described by Caldwell and Moloy.

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Bunster, E.: Uterine Intubation, Bol. Soc. chilena de obst. y ginec. **6**: 147, 1941.

The author discusses the uses and results with various rubber and metal intracervical tubes applied for stimulation of hypoplastic uteri, or in cases of malposition, dysmenorrhea, and sterility. Bunster feels that the mechanical stimulation of the cervix affects pituitary anterior lobe functions. He describes his modification of the Iribarne and Ségond tubes, essentially involving a funneled lower end, whose posterior rim is spout-lipped to lie in close apposition to the seminal pool. A slit in the cervix at 6 o'clock accommodates this portion of the funnel, which is held in place by 5 sutures. The author cites 12 cases in which the tube was used. Dysmenorrhea was relieved in most instances. Enlargement of the uterus and gain in body weight of about 2 kilos was common. Pregnancy occurred in some cases of sterility but the series is too small to evaluate in this respect.

R. J. WEISSMAN.

A SIMPLE APPARATUS FOR RESUSCITATION OF THE NEWBORN

F. A. D. Alexander, M.D., and Charles E. Martin, M.D.,
Albany, N. Y.

(From the Departments of Anesthesia and Gas Therapy and Administration, Albany Hospital and Albany Medical College)

ASPHYXIA neonatorum has been the subject of innumerable published articles. While many of these were devoted primarily to the etiologic and physiologic aspects of the subject, a great many more have been concerned with treatment, prophylactic and active. The large number and wide diversity of methods and procedures advocated indicate that no entirely satisfactory procedure has been reported. There is, however, agreement on some general principles underlying efforts at resuscitation of asphyxiated newborn infants. First, a patent airway must be established and maintained by aspiration, postural drainage, or some other means. Second, the body temperature must be preserved and trauma avoided, especially in premature infants. Finally, until respiratory efforts begin and pulmonary ventilation is adequate, the vital functions must be supported. It is in discussion of this last subject that most of the differences of opinion have arisen.

Establishment of pulmonary ventilation by artificial respiration of some sort is the most widely practiced procedure for resuscitation of the newborn infant. It is attempted by manual methods such as squeezing the chest of the infant, by the Sylvester, Schaeffer or other maneuvers, or by smartly slapping the back. Complicated, expensive and intricate mechanical devices designed to insufflate oxygen or carbon dioxide-oxygen mixtures into the lungs or to blow the gases in and suck them out intermittently are purchasable. Mouth-to-mouth insufflation of the infant with the physician's exhaled air is the oldest, most widely used and still most generally applicable and satisfactory method of artificial respiration for infants in the newborn period.

Mouth-to-mouth inflation, widely useful as it is, still has some limitations and shortcomings. It permits no accurate control of the pressure with which the lungs are inflated. Overdistention of the chest of newborn infants by too much pressure, whether from a mechanical apparatus or mouth-to-mouth inflation, may seriously damage the lungs. During the carrying out of insufflation by this method, the operator's face is so close to the infant that it is impossible to actually observe whether the chest or stomach is being inflated and palpation may be deceiving in this respect. No provision is made for the use of oxygen-rich or variable oxygen-carbon dioxide mixtures where they may be indicated or desirable. Some individuals find mouth-to-mouth inflation esthetically distasteful. The edentulousness of the newborn usually makes it necessary to insert the finger between the gums to improve the airway and this maneuver in turn increases the difficulty in establishing an airtight contact with the face.

DESCRIPTION OF APPARATUS

The apparatus here described (Figs. 1 and 2) is a simple and readily portable device designed to permit the application of the principles of

mouth-to-mouth inflation and to eliminate as far as possible the limitations and disadvantages of that method. It was originally intended for resuscitation of the newborn infant, but by the substitution of masks of larger sizes for the infant mask it has been found valuable in resuscitation of children and adults as well. It consists essentially of a hollow brass tube about seven inches in length and about 1¼ inches in diameter which has at one end a mouthpiece and at the other a slip joint of such

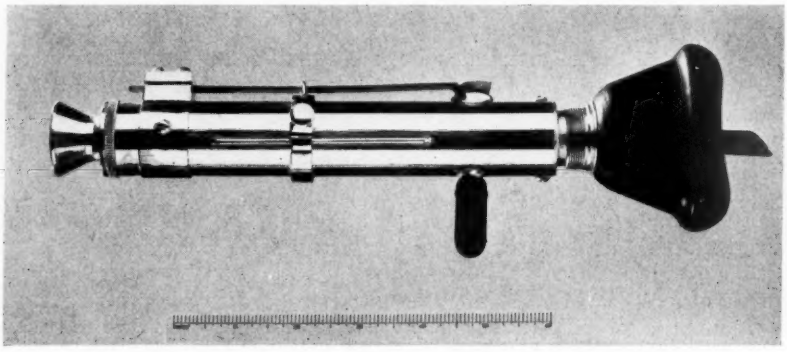

Fig. 1.—Apparatus assembled as used for full-term infants.

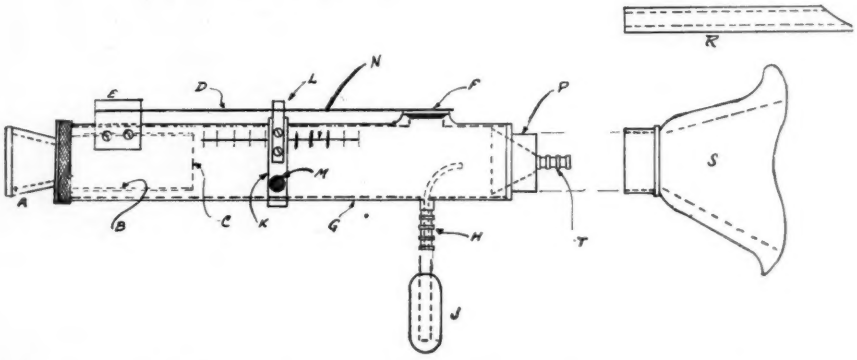

Fig. 2.—Cross section of construction. *A*, Mouthpiece. *B*, Brass capsule to be loosely filled with cotton gauze for filtration of exhalations. Sides of capsule solid but opens through gauze mesh *C*. *D*, Tension spring. *E*, Split block with set screws for securing fixed end of tension spring *D*. *F*, Tapered seated blow-off valve controlled by tension spring *D*. *G*, Brass tube 1/16 inch stock. *H*, Nipple for introduction of oxygen or for calibration of instrument using a mercury or water manometer. *J*, Rubber cover for nipple *H* when it is not in use. *K*, Sliding ring carrying rider *L* for varying tension on spring *D*. *M*, Thumbscrew for fixing sliding ring and rider in position on barrel *G* according to calibration scale *N*. *P*, Slip joint for attachment of infant's face mask or adult's face mask (not shown). *T*, Nipple for attachment of soft rubber airway *R* when its use is indicated or for attachment of an endotracheal catheter (not shown).

size as to fit anesthetic masks. Distal to the slip joint is a small nipple to which may be attached a rubber airway or a small endotracheal catheter when desirable. In the mouthpiece end of the tube, a cartridge with a wire gauze screen is inserted to provide a cotton filter for the insufflated air. Cotton is better than gauze because of its superior moisture absorbing qualities. Near the mask end of the tube is a side nipple to admit oxygen or carbon dioxide-oxygen or to calibrate the instrument. This is stoppered when not in use for these purposes. On the outside of the tube is a tension spring firmly attached at the mouth-

piece end, and ending in a tapered seat near the mask end, which covers an opening in the wall of the tube accurately and acts as a pressure exhaust control. The tension in the spring and therefore the pressure necessary to open the escape valve are controlled by a sliding ring carrying a rider over the spring. Along the side of the tube the pressure positions of the rider are calibrated.

METHODS OF USE

After each use the apparatus is sterilized by boiling in water. Between uses it is kept in a clean tray. When it is about to be used, sterile cotton is inserted into the cartridge and it, in turn, into the tube. The rider is adjusted toward the proximal (low pressure) end of the bar and then, holding the mask end, the mouthpiece is blown into two or three times to open the escape valve widely. When it is assured that the airway of the infant is patent, the mask is attached to the slip joint and the apparatus applied to the infant's face, so that the rubber airway intrudes into the infant's mouth between the gums and on top of the tongue. The mask is then adapted accurately to the face and held in place in the same manner as an anesthetic gas mask. The operator's small and fourth fingers, under the chin, tend to hold the infant's mandible forward while the rest of the hand holds the mask securely in place. The operator then rhythmically blows into the mouthpiece using a moderate, steady exhalation, such as one might use to blow on food to cool it. Between each insufflation the mouthpiece is removed from the mouth to permit the insufflated air to return from the infant's chest. Insufflation is at about the rate of 15 per minute. It should not be sharply expulsive exhalation or a cheek-puffing spurt of air which carries a wave of insufflation of high temporary pressure, but low volume. That the chest and not the stomach is being inflated may be determined by actual observation. When the child begins to make spontaneous respiratory efforts, it is usually unnecessary to continue the insufflation further, although if thought beneficial, oxygen may be added to the air being breathed by running it into the apparatus through the nipple near the mask end. In this case sufficient volume of oxygen should be introduced to wash out the carbon dioxide which might accumulate.

When it is thought advisable to use oxygen or carbon dioxide to insufflate before breathing has begun, it is carried out by admitting the gas through the side nipple and holding the palm of the hand over the mouthpiece end, placing it on and off rhythmically and intermittently in the same manner as the mouth-to-tube inflation described above. In this manner, the infant's lungs are intermittently inflated with the gas chosen. If it is deemed advisable to use an endotracheal catheter and insufflate the air or gas directly into the trachea, the mask and rubber airway are removed and the apparatus attached directly to the catheter at the small nipple on the mask end. For resuscitation of seriously asphyxiated infants, particularly of the pallid type, we prefer endotracheal insufflation. It must be remembered that if insufflation is made directly into the trachea less pressure will be needed to expand the lungs adequately than with the mask alone, or mask and airway.

SUMMARY

An apparatus is described to apply the principles of mouth-to-mouth insufflation for resuscitation of the newborn.

Its specific advantages are:

1. It facilitates the establishment of a patent respiratory airway.
2. It permits the use of a face mask designed to afford an airtight fit on the face, so as to be efficient.
3. Insufflation directly into the trachea can be provided by attaching the instrument to an endotracheal catheter at the small nipple in the mask end.
4. It is long enough to permit the operator to observe directly the amount of chest expansion occurring with each insufflation.
5. It contains a filter to afford some protection to the infant from infection through bacteria in the exhaled and insufflated air.
6. It provides accurate control of the pressure under which the insufflated air is blown into the infant's lungs.
7. Provision is afforded to insufflate oxygen or carbon dioxide-oxygen when they are considered desirable.
8. It is easily portable.
9. It can be readily sterilized.
10. It is simple to operate.
11. The pressure control spring and blow-off valve are simple in construction and unlikely to become deranged, damaged, inaccurate, or to need frequent recalibration.
12. This apparatus may be used for resuscitation of children or adults by substituting a proper size face mask for the infant's mask on the universal slip joint at the mask end.

NOTE.—Since this article was prepared the apparatus has been improved by the introduction of a guard bar over the top of the tension spring and by the substitution of a lucite mouthpiece attached to the filter cartridge and a substantial decrease in the weight of the instrument.

We are indebted to Mr. Gerard Buschenhenke who prepared the original model from submitted plans and to the Foregger Company of New York for material assistance in the calibration and testing of the instrument.

Burn and Withell: A Principle in Raspberry Leaves Which Relaxes Uterine Muscle, Lancet 2: 1, 1941.

Raspberry leaf tea has been a herbalist's remedy for many years. Pharmacologic study of water extracts of dried raspberry leaves demonstrates that they contain a principle which relaxes the smooth muscle of the uterus and intestine when this is in tone. The action is exerted in the body of the cat and also when the muscle is suspended in a bath. The relaxation produced in the body increases with successive doses. Apparently the same principle causes contractions of the uterus of the rabbit in situ and also of the isolated uterus of the cat, rabbit, and guinea pig when they are not in tone.

CARL P. HUBER.

Correspondence

Kymograph Records of Uterine Contractions

To the Editor:

In the May issue of this JOURNAL (47: 815, 1942) appears an article by William Bickers, entitled "A Study of Contractions in Labor Based on Kymographic Records Obtained From an Intrauterine Balloon." It is based on data from four patients. This article contains a statement of interest to me, since it misinterprets and attempts to disqualify certain views and facts which I have advanced. This would be of no significance were it not that several other investigators and clinicians have likewise misconstrued my views in this respect from time to time.

The above article states: "It has been suggested that the onset of labor may result from distention, which puts the muscle fibers under tension; ischemia results and contractions follow." This is represented as the view of the undersigned, as expressed in Chapter XII in my monograph, *Physiology of the Uterus* (Hoeber, 1939). It is dismissed by the following statement: "The well-known fact that artificial rupture of the membranes at term will induce labor tends to invalidate the distention theory as a cause of labor."

The facts of the situation are as follows: In the above-mentioned chapter, an evaluation is made of the physiologic relationships in the uterus at term. In the initial sentence, the following statement appears: "There is no known single cause for the onset of labor as the numerous theories of the past and present imply. Rather, it now seems that parturition begins as a result of the gradual, accelerating convergence of a number of factors, structural, humoral, nervous, nutritional, and circulatory, which, at a time characteristic for each species and adapted to the morphologic conditions present in each, are so associated that they lead to evacuation by the uterus of its contents." A clearly speculative, tentative and hypothetical set of physiologic relationships is then given diagrammatically. The scheme refers to distention factors (which clearly exist), hormonal factors (which have never been denied), metabolic conditions in the myometrium (that are seldom considered), the rudiments of simple muscle physiology (which are affected by either a balloon in the uterus at term, or by rapid loss of fluid from rupture of the membranes), and other factors. The following statement also appears: "Physiological coordinating factors—unknown." In the face of these factual considerations, a "distention *theory*" for the onset of labor, based on these views written in 1938 and published early in 1939, is ascribed to me today. ***There is no "distention theory."***

To quote my views more correctly, Dr. Bickers should have referred to a paper entitled: "Physical Conditions in the Uterus Governing the Duration of Pregnancy," published late in 1939 (*Anatomical Record* 75: 175-190). The essence of this work, established by measurements, is that until shortly before the onset of labor, the tensions on the uterine wall are different in different parts; this is apparently provided for by several mechanisms, structural, physical, and hormonal. As term approaches, the "slack" is progressively taken up, and the maximal uterine tension becomes about uniform over the surface of the whole organ. The significance of this condition is given in the following quotation: "This appears to be, accordingly, the physical condition at the end of gestation which signals impending parturition." But what happens later, amid a complexity of conditions, to effect coordination of uterine contractions in labor remains as unknown as ever. Conse-

quently the effect of rupture of the membranes in early labor, or even at term after the physical conditions described above are attained, cannot be evaluated at present. To use it as an argument against a theory which has never been promulgated is, therefore, unjustifiable.

SAMUEL R. M. REYNOLDS, PH.D.

DEPARTMENT OF EMBRYOLOGY,
CARNEGIE INSTITUTION OF WASHINGTON.

Reply by Dr. Bickers

To the Editor:

I wish to take this opportunity to reply to Dr. S. R. M. Reynolds.

Dr. Reynolds apparently is concerned because he feels that I have attempted to disqualify certain statements which he has made regarding the cause of the onset of labor. It was not my intention to suggest that Dr. Reynolds believes that the distention factor is the only mechanism operating in the onset of labor contractions. Since my study was confined purely to the mechanical factors and made no attempt to investigate the endocrine, humoral, and cytologic changes, I was interested only in the physiologic alterations due to change in the intrauterine pressure.

I have studied Dr. Reynolds' letter with a great deal of care and frankly must admit that I cannot quite make him out. It will be noted from my paper that my language was very conservative. I said, "It has been *suggested* that the onset of labor may result from distention." Later I said, "Artificial rupture of membranes at term will induce labor which *tends* to invalidate the distention theory." I think that no one will deny the accuracy of these statements. I did not mention all of the other factors related to the onset of labor because they were not in the scope of this study.

Dr. Reynolds' more recent publication, which describes the increased uterine tension near term, is a real contribution to the subject and my investigations, not yet published, are thoroughly in accord with his. I cannot agree with Dr. Reynolds when he says that artificial rupture of membranes and its effects, which are so well known, cannot be used as an argument against the distention theory.

WILLIAM BICKERS, M.D.

RICHMOND, VA.

The sudden and untimely death of Dr. Hugo Ehrenfest occurred on July 24. An obituary will appear in the next issue of the JOURNAL.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Mammary Glands

Engel, Stefan: Anatomy of the Lactating Breast, Brit. J. Child. Dis. **38**: 14, 1941.

Impossibility or reduced ability of breast feeding is influenced by many factors. There are not only the physical state of the mother, nutrition, occupation, fatigue, etc., but also hormonal and psychical conditions to be taken into consideration. Also the stimulus of suckling is an important factor. The basic condition, however, is the milk-producing gland itself, which, in view of obvious difficulties so far, has not been sufficiently studied from the anatomic viewpoint.

In this paper the author reports careful investigations made on the breasts of 26 women who had died during labor or within the next few days. These investigations showed considerable differences in the structure of lactating breasts, varying from the normal breasts to those provided only with a small or even negligible amount of glandular tissue. Functional inability therefore often is fully explained morphologically, a point of great importance for therapeutic efforts to increase the milk output.

HUGO EHRENFEST.

Fredrikson, H.: Endocrine Factors Involved in the Development and Function of the Mammary Glands, Acta obst. et gynec. Scandinav. **20**: 293, 1940.

From experimental studies on rabbits, Fredrikson concludes that in the absence of the pituitary gland, the development of the breasts is directly dependent on the action of the ovarian hormones. In addition, he has shown that the purified preparation of prolactin, which exhibits no gonadotropic, thyrotropic or adrenal activity can induce lactation in spite of the absence of the pituitary gland. Therefore, this prolactin can be substituted for the anterior lobe of the pituitary with regard to the excitation of lactation.

J. P. GREENHILL.

Feldweg, P.: Contribution to the Physiology of Nursing, Zentralbl. f. Gynäk. **65**: 585, 1941.

Feldweg believes that all newborn infants should receive mother's milk, and if the supply is not sufficient, it should be supplemented by wet nurse milk. The mortality of infants on artificial food is five to ten times as great as of those receiving breast milk. According to the author's figures, about 3 per cent of all nursing infants die during their first year as opposed to a 15 to 30 per cent mortality of nonnursing or poorly nursed infants. The average clinic in which 50 to

80 per cent of infants are nursed may expect a first-year mortality of 4 per cent at least. Poor nursing has a greater infant mortality than poor delivery. The author emphasizes that pumping the breasts after nursing keeps up full production of milk. The milk intake of 1,720 spontaneously newborn infants was studied through their second to ninth days, as well as the residual milk pumped from the breasts after nursing. Maternal production in general showed a much greater fluctuation than infant intake. More women had excess milk than deficient production. Of primiparas, those under 20 had quantitatively the best production. In multiparas milk secretion increased with parity. The onset of lactation occurs sooner in younger women and in multiparas. After spontaneous delivery, 90 per cent of this series of women were capable of nursing their infants.

R. J. WEISSMAN.

Folley, S. J., and Young, F. G.: Prolactin as a Specific Lactogenic Hormone, Lancet **1**: 380, 1941.

The authors review the available information concerning the role of the anterior pituitary gland in the production of lactation and emphasize that there are differences between the pigeon crop gland-stimulating (prolactin) and galactopoietic activities of anterior pituitary extracts. These differences are important in considering the clinical use of anterior pituitary preparations in women in whom lactation is deficient and perhaps explain differences in clinical results reported by various authors as the preparations used have been assayed for prolactin effect only. The authors suggest testing such materials for their galactopoietic effect on mammals.

CARL P. HUBER.

Fauvet, E.: Study of Lactation, Zentralbl. f. Gynäk. **65**: 580, 1941.

The author feels that the goal of those attempting endocrine control of lactation is unattainable. Many workers lose sight of the stimulating effect of suckling. Fauvet covered half the teats of a group of nursing dogs with tape and compared the resulting typical microscopic picture of a regressive mammary gland with that of the normally active glands thirteen and fourteen days after delivery. When the pups were allowed to suckle the previously covered breasts, they returned to full functional activity. From this standpoint, says Fauvet, the problem is not as dependent on the action of lactogenic hormone as endocrinologists would have us believe. As with cows, full function of the glands depends on a nourishing diet and complete emptying of the breasts.

R. J. WEISSMAN.

Lehmann, G.: A New Means of Increasing Lactation During the Puerperium, Zentralbl. f. Gynäk. **64**: 1480, 1940.

Lehmann reviews briefly the endocrinology and physiology of lactation. The lactation inhibiting effect of follicle hormone is well understood. In cases in which renal excretion of the hormone is delayed post partum, lactation is usually inhibited. In 1,056 uncomplicated births, lactation was adequate in 82 per cent. In 20 eclamptics, lactation was adequate in 25 per cent. These findings gave the author the notion of administering a purine diuretic in cases of poor or average lactation, in order to increase the rate of renal elimination of the follicle hormone. As an added proof of the author's premise, it was found that abundance of lactation was in direct relation to the amount of blood lost at delivery. In the group of mothers losing over 1,500 Gm. of blood all had abundant lactation.

Novophyllin was given to 64 mothers in 3 doses in the first twelve hours post partum. Each received 1,500 c.c. total fluids daily. There was a notable average increase in both amount and specific gravity of the urine. Then the drug was given to a group of 396 mothers; 93.2 per cent had abundant lactation and 6.8 per cent moderate lactation. An untreated group of 539 mothers had abundant lactation in 72.0 per cent, moderate in 27.6 per cent, and no lactation in 0.2 per cent. Larger doses of the diuretic increased the percentage of those said to have abundant lactation. Comparison of the daily average milk secretion showed the diuretic treated mothers to be secreting 13 to 123 Gm. more milk per day. The effect of the medication was definitely evident up through the ninth post-partum day. The weight of children on the ninth day was 30 per cent in excess of birth weight as compared with an increase of 15 per cent for the children of untreated mothers. Lehmann felt that his results were good enough so that there was no need of risking a trial with mercurial diuretics. If the medication works too well the secretion can be controlled by small doses of follicle hormone.

R. J. WEISSMAN.

Menju, K.: The Effect of Visible Light Upon the Secretion of Milk, Jap. J. Obst. & Gynec. **23**: 130, 1940.

In cases in which the breasts were irradiated with infrared rays, the secretion of milk was increased. On the other hand, irradiation of the breasts with blue rays retarded the flow of milk. Irradiation with white light had no effect. When the heads of experimental animals were subjected to irradiation with infrared rays, the flow of milk was increased, but no effect was observed when the blue or white rays were used. The author concludes that the effect of light on the secretion of milk is produced by way of the vegetative nervous system and the endocrine glands.

J. P. GREENHILL.

Olsen, A.: Nursing Under Conditions of Thirst or Excessive Ingestion of Fluids, Acta obst. et gynec. Scandinav. **20**: 313, 1940.

Thirteen nursing mothers were given daily amounts of fluid varying from 600 to 2,775 c.c. and daily determinations were made of the total amount of breast milk obtained. Only one of the 13 women showed a parallelism between the increase in the amount of fluid taken and the increased production of milk. In all the others there was no such relation between the fluid intake and the milk output observed. Five women were very thirsty when their fluids were restricted, but this had no effect on the amount of milk excreted. In fact, one of these women had a remarkable increase in milk. The infants showed no effect from restriction of fluids in the mother. The author concludes that the supply of breast milk cannot be increased by having a woman take more fluid nor can the amount of milk be cut down by curtailing the ingestion of fluids.

J. P. GREENHILL.

Gilber, Barton: Persistent Lactation With a Note on Chiari and Frommel's Disease, Brit. M. J. **2**: 305, 1941.

The history of a 35-year-old married woman showing lactation continuing over fifteen years following childbirth is reported. She had persistently manipulated or expressed her breasts during this time believing it normal to lactate the entire reproductive period following childbirth. Her menses had recurred six months after childbirth at monthly intervals, lasting four days with each period. Physical

examination revealed voluminous breasts. A few red blood cells were present in the milk first obtained from the left breast. The uterus was slightly smaller than normal, firm, and in normal position.

Chiari and Frommel's disease exhibits persistent lactation associated with uteroovarian atrophy, the degree of atrophy varying in different cases. Menstruation may not recur after weaning, depending on the degree of atrophy.

The case presented is not regarded as true Chiari or Frommel's disease since the uteroovarian atrophy was of minor nature. The daily manipulation of the breasts may have been quite influential in prolonging lactation.

FRED L. ADAIR AND WILLIAM ROSENBAUM.

Anderson, A. B., and Brown, Alexander: Tetany Following Prolonged Lactation on a Deficient Diet, Lancet **2:** 482, 1941.

The authors report a patient, 42 years of age, para ii, who developed definite tetany during a lactation period of twenty-one months. Her diet had been inadequate. Treatment with a high-calcium milk diet resulted in rapid recovery and was in striking contrast to the lack of response to therapy in those cases where tetany is due to failure of calcium absorption. The authors suggest that calcium deficiency is common in lactating women.

CARL P. HUBER.

Spoor, Hartman, and Brownell: Cortilactin, the Lactation Factor of the Adrenal, Am. J. Physiol. **134:** 12, 1941.

A lactation factor was prepared from the adrenals by isoelectric precipitation. The pigeon crop gland response was used for its assay. The best cortilactin preparation possessed about one-tenth of the potency of purified prolactin when tested by the crop gland method. The daily injection of 1 mg. of the cortilactin preparation into an adrenalectomized female rat, maintained on cortin, enabled her to lactate normally.

J. P. GREENHILL.

Preissecker, E.: Influence of Male Sex Hormone on the Female Breast, Zentralbl. f. Gynäk. **64:** 999, 1940.

The author gave "physiologic" doses of testosterone to nursing mothers at periods varying from ten days to three months post partum. An increase in milk secretion was noted in all cases, in his opinion as a result of the antagonism of testosterone to the lactation inhibiting follicular hormone.

R. J. WEISSMAN.

Nathanson, Meigs, and Parsons: The Treatment of Mammary Pain and Secretion With Testosterone Propionate, New England J. Med. **226:** 323, 1942.

Testosterone propionate was administered to 30 carefully selected patients with severe mammary pain and secretion. It was found to be an effective agent in the relief of the syndromes in a high percentage of the cases. It appears to be more efficient than the estrogenic hormone in the treatment of the same lesions. Recurrence of symptoms is the rule, usually within six months after medication is discontinued. Prolonged and continuous treatment especially with large doses is to be discouraged. Periods of treatment should be followed by adequate rest

periods. Many patients present a dominant psychogenic element, and others have spontaneous remissions, therefore, patients should be carefully selected for this treatment.

HUGO EHRENFEST.

Duffy, Paul V., and Corsaro, Joseph: Suppression of Lactation by Testosterone, J. A. M. A. **116**: 33, 1941.

The authors report encouraging results by the use of testosterone in the suppression of lactation post partum. In 18 cases in which the breasts were definitely engorged, tender, and painful, the administration of testosterone was begun on the third or fourth day post partum. Dosage ranged from 15 to 75 mg., the largest quantity given at any single injection being 25 mg. Tenderness was relieved promptly, and lactation was suppressed in twenty-four to forty-eight hours. Similar quantities of testosterone were ineffective in suppressing lactation in 4 cases in which it had already been definitely established when treatment was begun. The treatment also failed in 3 cases in which 25 mg. were administered immediately after delivery. It has been found that methyl testosterone given orally will produce comparable results (25 mg. three times daily for 6 doses).

It appears that the pituitary depression caused by moderate doses of testosterone administered at the initiation of the secretory phase of the breasts is sufficient to inhibit lactogenic function of the pituitary gland and to suppress lactation.

WILLIAM BERMAN.

Fleischer and Kushner: Inhibition of Lactation. Percutaneous Use of Testosterone, J. Clin. Endocrinol. **1**: 407, 1941.

Studies of the authors showed that male sex hormone administered by inunction was effective in 68 per cent of cases in whom for one reason or another inhibition of lactation was desirable. It was only partially effective in 29 per cent of the cases. It was entirely without effect in 3 per cent. In no case was lactation entirely arrested. The effect was rather a diminution in the degree of lactation with resulting diminution of secondary signs and symptoms, such as engorgement and pain. Testosterone, percutaneously, can successfully be used for the inhibition of lactation.

J. P. GREENHILL.

Spence, A. W.: Local Inunction of Testosterone in Chronic Mastitis, Lancet **2**: 387, 1940.

Testosterone or testosterone propionate administered by inunction in daily doses of 3 to 10 mg. gave relief of pain to 8 patients with chronic mastitis. In 2 patients relief was obtained with inert ointment as well, but in the remaining 6 this was ineffective. The author points to the small dosages and absence of side-effects as advantages of this method in comparison with similar therapy by injection.

CARL P. HUBER.

Folley, S. J.: Effects of Estrogens on Lactation, Lancet **1**: 40, 1941.

It is now an accepted fact that the administration of estrogen stimulates growth of the mammary ducts and in some species the lobule-alveolar system, though it is not clear whether the effect is direct or is mediated through the anterior pituitary. It is further known that estrogens will inhibit lactation. This occurs whether or

not the ovaries are present. At least one androgen, testosterone, also inhibits lactation and has the power of stimulating mammary growth.

Estrogens are also capable, under suitable conditions, of enhancing milk secretion by increasing the concentration of both fatty and nonfatty solids. The threshold for the enrichment effect is lower than for inhibition. These two effects are more readily separable with natural estrogens than with diethylstilbestrol.

CARL P. HUBER.

Noble, R. L., and Collip, J. B.: Regression of Oestrogen Induced Mammary Tumours in Female Rats Following Removal of the Stimulus, Canad. M. A. J. **44**: 1, 1941.

Mammary tumors produced in rats by the subcutaneous implantation of estrone pellets showed marked cellular hyperplasia but were all localized and showed little tendency to invade the stroma or adjacent tissue. Continuous growth occurs until the animal's death, provided the pellets remain intact. Attempts to transplant the tumors into other rats have failed but in two cases homotransplants grew successfully. Lung metastases were found in one rat with advanced tumor formation of nine months' duration. Cellular infiltration of a typically malignant appearance was encountered in a few cases. Four rats treated with progesterone showed cessation of tumor growth. In 4 rats from whom the estrone pellets were removed, the tumors completely regressed. One of these animals had an ulcerated primary mammary tumor with a histologic picture of malignancy and a successful homotransplant. After long periods nearly all animals were found to have large pituitary adenomas, and in 2 rats large hemorrhagic adenomas developed during the first year of treatment.

CARL P. HUBER.

Wirth, Karl, and Peters, Max: Report on the Roentgen Ray Treatment of Early Puerperal Mastitis, München. med. Wchnschr. **86**: 59, 1939.

Wirth and Peters present their results and experiences in treating patients with an early infiltrative mastitis by using soft roentgen rays, giving 10 to 20 per cent skin erythema doses. Treatment, they believe, must begin within forty-eight hours of the onset of symptoms. In patients in whom infiltrations have occurred and nodules have formed, and in cases of interstitial mastitis the roentgen ray treatment promises but little success; in fact, it may even lead to more necrosis of the tissues thus causing retardation of recovery because of the chronic, inflammatory edema resulting.

The value of using roentgen therapy in the early cases must not be overestimated, however, since these inflammations also recede quickly under ordinary treatment. The advantages of the roentgen therapy lie in the fact that pain disappears quickly and the patient is able to continue nursing her baby.

C. E. PROSHEK.

Antoine, T.: Endocrine Influences on Lactation, Zentralbl. f. Gynäk. **65**: 465, 1941.

The author emphasizes that the problem of regulating lactation therapeutically is a complex one depending upon the multiple influences initiating lactation in the first place. With some of the endocrines now available the problem is mainly one of dosage, while with others the mechanism of inhibition or increase of lactation is obscure. The vitamin status of the gravid and post-partum woman is of more than minor significance.

The author gave *stilbene* (Cyren) to 80 post-partum women who did not wish to nurse their infants, beginning the first puerperal day. Of them 47 received the drug in ointment form percutaneously, while the remainder required either 10 mg. doses intramuscularly or 12 mg. by mouth, to inhibit lactation. In another group of women, breast fullness and pain was relieved by doses of 0.75 mg. intramuscularly. Percutaneous application of the ointment to only one breast was effective. The unmedicated breast gave no evidence of swelling or lactation.

In the author's clinic 207 women received *progynon* in doses from 50,000 to 600,000 units, averaging 100,000 to 500,000, in the last weeks of pregnancy; 86 per cent were able to nurse their infants, the rest had their offspring on complementary feeding or on full formula. High doses are not to be feared.

Conflicting reports of the effect of *testosterone* on lactation should not discourage further work along this line, for the answer here lies in sufficient dosage. Antoine suggests an analogy of the inhibitory effect of pituitary irradiation on menorrhagia and the stimulating effect of light doses in amenorrhea.

Diuretic therapy has been found effective in cases of insufficient lactation. Thyroid as well as *purines* have been given with excellent results. *Prolactin* has failed with many, principally because of low dosage. When prolactin fails in spite of high doses, one must look to estrone and progesterone deficiencies which have failed to develop a competent glandular structure. Prolactin, incidentally, has been found in most of the organs and tissues of man; in the placenta from the third to eighth months, in the decidua, in the fluid of hydatid moles, also in newborn infants.

R. J. WEISSMAN.

Item

American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 13, 1943, at 2 P.M. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year. All applications must be in the office of the Secretary by November 16, 1942.

Effective this year there will be only one general classification of candidates, all now being required to have been out of medical school not less than eight years, having in that time completed an approved one year general rotating interneship and at least three years of approved special formal training, or its equivalent, in the seven years following the interne year. This Board's requirements for internships and special training are similar to those of the American Medical Association since the Board and the A. M. A. are at present cooperating in a survey of acceptable institutions. All candidates must be full citizens of the United States or Canada before being eligible for admission to examinations.

All candidates will be required to take the Part I examination, which consists of a written examination and the submission of twenty-five (25) case history abstracts, and the Part II examination (oral-clinical and pathology examination). The Part I examination will be arranged so that the candidate may take it at or near his place of residence, while the Part II examination will be held late in May, 1943, in that city nearest to the largest group of applicants. Time and place of this latter will be announced later.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Candidates certified (total 185) by American Board of Obstetrics and Gynecology at the June, 1942, examination held at Atlantic City, N. J.

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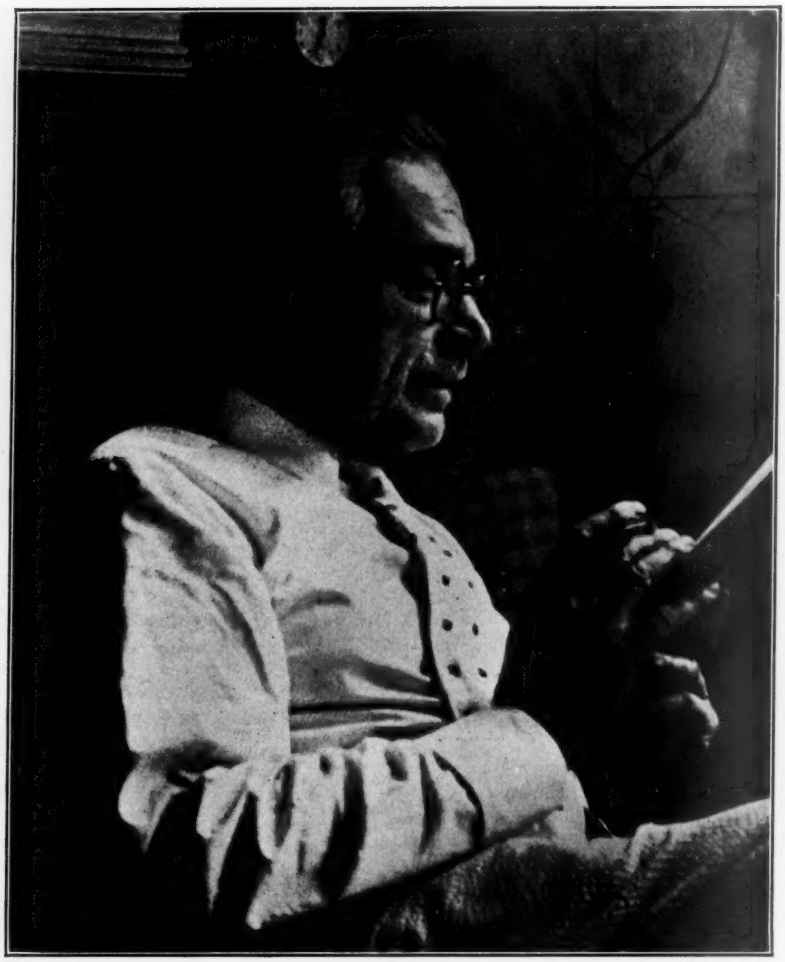
*Deceased, June 18, 1942.

Erratum

In the review of the book on "Hernia" in the May, 1942, issue of the JOURNAL, page 904, the author's name should be "Iason" instead of "Jason."



Hugo Ehrenfest
1870—1942